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ORIGINAL ARTICLES

CULTIVATION AND COORDINATION OF CLINICAL RESEARCH*

By Robert H. Williams, M.D.

EXECUTIVE OFFICER AND PROFESSOR OF MEDICINE, UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON

Many full-time clinical staff members, such as the Author, are so busily engaged in immediate problems of teaching and research that we participate far too little in the major policies affecting these activities. Some of the problems and methods for approaching them are presented in this paper.

Some Problems of Full-time Clinical Teacher-Investigators. In order to consider carefully the problems that face us, we should review the requirements for excellent clinical teaching and research. We must have well-trained staff members, with the appropriate philosophy, who have adequate time and facilities for teaching and research[6], and optimal conditions for selecting and educating students, interns, residents and research fellows. We must have the power to select and control patients, offer good patient care, and have excellent laboratory facilities. Anyone who is fully familiar with the problem knows that these conditions can be optimal only when there are excellent relations with granting agencies, the public, the patients, the practicing physicians, the hospital administration, the nurses, dieticians and others.

In the following sections are discussed a few of the problems that either confront us now or probably will in the future. These include (1) the relationships of full-time staff members with part-time staffs, (2) relationships with the public, (3) financing research, (4) staff working conditions, (5) research training programs, and (6) conjoint teaching programs.

1) RELATIONSHIPS WITH PART-TIME STAFFS. In many institutions there are wide chasms between the activities of the full-time and the part-time staff, to the loss of each group. Little reflection is required to recall numerous outstanding research contributions made by part-time staff members. Whereas it is true that, because they lack the time, they cannot perform many complicated laboratory procedures as efficiently as can the full-time staff, part-time staff members can conduct numerous clinical investigations very effectively. Moreover, we, the full-time staff, need the part-time staff very much in our teaching programs, in many of our ex-

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periences with patients, and in dealing with legislators and certain granting agents. A problem which has arisen in some medical school towns, and one that has generated much friction between the part-time and full-time staff, relates to competition in private practice. Some university hospitals have been accused of indulging in corporate practice, fee-splitting, socialized medicine, and so forth. At a national level, great attention is incited by a proposal made by practicing physicians and now being studied by the American Medical Association Council on Medical Service to prohibit university hospitals from accepting private patients. This is a matter of great concern to us since the number of indigent patients is rapidly decreasing, because of the great increase in various medical health insurance plans and many governmental health plans. We will have to depend more and more upon the use of private patients for teaching and research. We need very much the help and cooperation of the practitioners in this matter. Conversely, we can do a great deal to aid this group of colleagues and we should certainly do it. We must establish a mutually profitable relationship; one that does not mortgage education, research or other activities.

2) RELATIONSHIPS WITH THE PUBLIC. Whereas the average practicing physician may not have as close a relationship with his patient today as physicians had in the previous generation, the investigator is probably accorded the highest esteem ever, because of the numerous discoveries being made. We have at our disposal great financial resources and many volunteers as experimental subjects, but in accepting these, we are assuming great responsibilities for which we are held accountable. Now, a good many physicians are very much concerned by the potential danger to which certain patients, knowingly or unknowingly, are subjected. Some of the procedures have no possible direct benefit to the patient. "In a great zeal for knowledge, potentially dangerous experiments may be done without the subjects' knowledge or permission. The patient, however humble and however ill, in whatever degree derelict and forlorn, has sacred rights which the physician must always put ahead of his burning curiosity," writes Bean[1].

The lay public has been of great aid in raising funds, by putting on drives, by influencing legislators, and in other ways. However, it is important for us to help work out better methods for the distribution of funds, ones more proportionate to the needs than to the dramatizations. We should also acquaint the public with the fact that immediate returns on the investments rarely occur.

3) FINANCING RESEARCH. Much of the clinical research today is "big business" and draws funds from numerous sources, particularly from (a) government, (b) public drives, (c) private foundations and (d) pharmaceutical companies. Since most of the fund-raisers do not engage in clinical research, clinical investigators should play a major role in the formulation of the policies governing the use of the funds. Great caution must be exercised in accepting money that necessitates investigations in what seem to be less appropriate fields or that interferes with a good long-range balance between teaching and research. We need to encourage more support of the competent investigators and to place less reliance upon project description; however, definite improvement along this line has occurred in the last few years.

4) STAFF WORKING CONDITIONS. There should be appropriate academic titles, salaries, clinical and laboratory facilities, academic freedom and time for

meditative gestation. A common problem is that full-time staff members must see too many patients in order to receive an appropriate income. Indeed, in some institutions the clinical staff has to support the basic scientists and provide for many of the other expenditures for teaching and research. Often, in such situations, the faculty title is superior to the academic merits of the physician, an undesirable condition. In several medical schools I have seen this clinical service function enormously handicap the teaching and research programs.

In recent years, with the greatly increased employment of complex techniques in research, it has become distinctly advantageous to appoint to the staff of clinical departments certain basic scientists, particularly biochemists and physicists, who work as colleagues in team research. This group makes very important contributions, not only by research but also by teaching the fundamental principles of research to research fellows, our future academic staff. Therefore, the significant role of this group must be appreciated throughout all segments of our universities and granting agencies.

5) RESEARCH TRAINING PROGRAMS. To become an outstanding clinical investigator requires great skill in each of three directions: (a) clinical wisdom, (b) human relationships, and (c) scientific critique. The extent of the honor and the art associated with the *clinical* phase of research must be reemphasized to some of our colleagues who become so entangled in a maze of expensive apparatus and complex techniques that they either lose perspective or interest in the ultimate clinical objectives.

Those of us who are attempting to *cultivate* clinical investigation, know that we must be interested in all phases of education of students and graduates. We are concerned with their inspiration, their ultimate objectives, their philosophies, their attitude toward research, and their approaches in solving problems in medicine, as well as the facts that they learn. Therefore, the way that the various courses in basic sciences and clinical sciences are integrated is an important consideration for us, as is the amount of social science, home care, general practice preceptorships and numerous other phases of the teaching program. Since the training of interns and residents is also of great concern to us, we should be playing an important role in considerations of the proposal that all internships should be rotating. Likewise, we should be very much concerned with the influence of the Specialty Boards on medical education; a few of the smaller specialties are extortionists.

We are interested in the *education* as well as the *training* of clinical investigators, and want to help them attain most effectively the goals for which they are best suited, and while attempting to develop better scientists, we want to develop better men.

Much progress could be made in the selection of physicians for a career in clinical investigation and in the education that is offered them. The approaches along these lines have been haphazard. There should be discussions of "the philosophy of research, its principles, the meanings of 'chance,' 'probability,' 'randomization,' etc., the design and expedition of controlled research and the limitations of mind," writes Ingle[3]. Evidence of the inadequate applications of statistical methods and control studies is in the report of Ross[5] who found in reviewing 100 articles from 5 leading American journals that 45 studies had no controls and 18 were inadequately controlled.

As Kubie[4] has emphasized, a great deal of worthwhile information could be obtained by conducting research upon the researcher. Such information would doubtless help in the selection of individuals to engage in research and in the formulation of the most effective program for research. In addition to acquainting our research fellows with the cold objective techniques for scientific accuracy and progress, we should inculcate a spirit of warm human understanding, social responsibility and moral integrity.

In recent years the amount of team research has increased greatly, because many of the major studies present intricacies that constitute a herculean problem for the lone investigator to solve. However, team research introduces many problems, such as freedom for intellectual pursuit by individuals, appropriate distribution of credit and proper cooperation. Even with team research there should be opportunity for the individual to pursue his own curiosity while cooperating in the pursuit of a common goal. It is important that we have specialists in restricted fields, but the threads of knowledge must be collected frequently and woven into conceptual patterns revealing scientific laws, thereby becoming meaningful and usable. The perception of these laws is hastened by the application of creative imagination; just as in solving a jig-saw puzzle, one fits the pieces individually but the process is hastened by imagining what the different color shades might form. Efforts to be practical need not hamper the search for fundamental truths, as has been demonstrated by Pasteur and many others. Indeed, a practical objective tends to stimulate the scientist to attempt to fit all the facts together. "He who attempts only to gather facts," writes Bronk[2] "deals with the bare bones of science, unarticulated and unclothed with the flesh of meaning." The facts may be only confusing until they are put together so that they form a coherent pattern.

6) CONJOINT TEACHING PROGRAMS. If medical students are to be educated in the most efficient manner, the teaching program must be well coordinated. The development of the numerous specialties and subspecialties and particularly the defensive reaction of the smaller specialties has resulted in a program chopped into a great many small blocks with much duplication and confusion. Undoubtedly, the training programs should be reorganized with the main objective being to indoctrinate the student in the appropriate principles and approaches so that he can adjust satisfactorily as new knowledge is discovered and some phases become obsolete. His training should include orientation regarding some of the major principles of research, because some of these need to be applied in practice. The craving for new knowledge and the implications of improvement in diagnosis and treatment constitute some of the most scintillating stimuli in medicine.

There is a very great need for systematic research in teaching including many more objective evaluations of the effectiveness of specific teaching methods and individual teachers. Many who are highly scientific in the laboratory are often quite nonscientific in evaluating teaching and display much more dogmatism than knowledge.

Formulation of Major Policies in Teaching and Research. We, the members of the American Society for Clinical Investigation, are probably the most active clinical investigators and teachers of any group in the world, but as a group, how much do we contribute to the formulation of the major policies under which we work? The answer is, of course, very little. The

need for this participation is rapidly increasing.

Some of the agencies that have been mainly concerned with the formulation of the policies are shown in Fig. 1. The Association of American Medical Colleges (A.A.M.C.) and the A.M.A. Council on Medical Education and Hospitals (C.M.E. & H.) have been excellent consultants, although their number has been limited. Moreover, it is important that we approach the problems from our own point of view. The activities of the granting agencies and the A.A.M.C. and the C.M.E. & H. have been somewhat interdigitated, but less than they should be. There is considerably less interdigitation of the

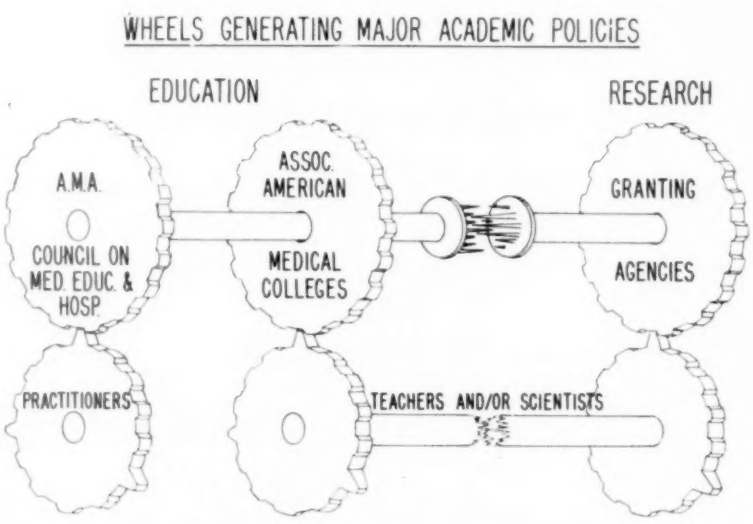

Fig. 1.—For many years the American Medical Association's Council on Medical Education and Hospitals and the Association of American Medical Colleges have worked closely together in the formulation of major policies in education. As illustrated above, relatively very few practitioners, teachers and scientists have extended their activities sufficiently to exert directly a very significant influence on the two "big wheels" (C.M.E. & H. and A.A.M.C.) generating major policies. This may be attributed to negligence rather than to lack of opportunity. The granting agencies direct significantly the course of research, with insufficient contributions from the active investigators; there are some exceptions, of course. Much greater over-all efficiency would also result by a better application of energies in research to teaching and *vice versa*. There is need for better integration of the actions of the granting agencies with those of the A.A.M.C. and the C.M.E. & H. The active investigators and teachers also suffer from a lack of coordination of their activities.

doing a good job for many years to improve medical education. Moreover, the two agencies have been coordinating their activities very nicely. Thus far they have concerned themselves relatively little with research. The various granting agencies have played a major role in formulating policies relative to research. They have had some activities of teacher-scientists with these three groups than is desirable. As mentioned earlier, there is insufficient collaboration of the full-time staff members with the practitioners. The activities of all of these groups should be better coordinated. Energies expended in research become more efficiently used when simultaneously ap-

plied to teaching and *vice versa*; the two activities should be more synergistic.

The fact that we have not been more active in the formulation of the major policies is not the fault of the three "big wheels" shown in Fig. 1, but our own. There is a common notion that it is a pity to waste the time of an investigator on administrative matters, but many instances illustrate that certain scientists have contributed far more to progress in science by their administrative feats than through their contributions in the laboratory (for example, Doctor Welch). It is true that one cannot engage extensively in teaching, research, administration, public relations, policy committees, and so on. An attempt at such would merely lead to a physical presence and a physiological absence, a sort of "cancer of academic medicine."

We of the clinical sciences have an enormous amount of work to perform and responsibilities in many directions. Indeed, it is just these factors that make it necessary to organize our activities as efficiently as possible. To leave our problems in a hit-or-miss state is not sound. At least some of us should get together periodically to discuss the best plans for proceeding. In replying to my letter, sent to all members of the Society, many deemed it important that small groups meet annually at the time of, but independent of, the Society meeting. They also indicated that certain items of business could subsequently be presented to the Society for informational purposes or for Society action. I have also encountered members of the Association of American Physicians who were interested in such discussions. Consequently I have planned to invite small groups to meet as study sections and subsequently as a larger group, for general discussions. At the latter gathering I hope that we may also have representatives from the

TABLE OF ACADEMIC POLICIES

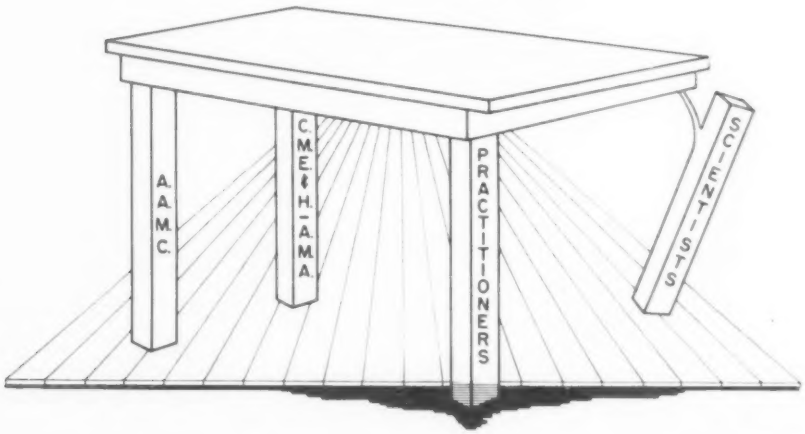

Fig. 2.—Note that the scientists are giving only a "splinter" of support to the table of academic policies. The practitioners are somewhat "mired down" because the majority have little interest or information relative to the problems of academic medicine; a few of them have been very helpful.

A.A.M.C., the C.M.E. & H., the granting agencies and other groups who can keep us informed on their objectives; mutual advantages should result. I also hope that more of us can attend the deliberations of their respective groups. I do not believe that the plans I have presented will be resented by these other groups. On the contrary, they probably will say it is about time that we help them with the load; thus far it has been carried chiefly by the A.A.M.C. and the C.M.E. & H. We have given only a splinter of support to the table of academic policies (Fig. 2). The practitioners have mired down because of the lack of clear and wise objectives, emphasizing again the need for mutual understanding and coordination of activities. Some of them of course, have been very helpful.

Conclusion. We, the full-time clinical teacher-investigators, must handle effectively numerous factors in developing optimal programs in teaching and research. Some of these have been discussed in detail in this paper. Whereas certain duties are unpleasant they must be dealt with squarely. While we sit working peacefully at teaching and research in our ivory towers, unconscious of what lies outside, rising tides of revolutionary policies are beginning to surround us and if we don't become alert and help direct the force of these silent, powerful waves, we will abide in a dinghy pulled by careless captains.

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CONCLUSION IN INTERLINGUA

Cultivation e Coordination de Recercas Clinic

Nos, qui es exclusivemente instructores-investigatores clinic, debe monstrar nos efficace in manipular le numerose factores involvite in le disveloppamento de optime programmas de inseniamento e recerca. Alicunes inter iste factores es discutite in detalio in le presente articulo. Ben que certe deberes in iste complexo es pauco placente, illos debe esser complite lovalmente. Durante que nos labora pacibilemente in nostre eremiteria, insciente de lo que eveni al extero, crescente undas de tendentias revolutionari comencia inveloppar nos, e si nos non deveni alerte e contribue al domation del fortias de iste silente e forte undas, nos va trovar nos navigante le mares in debile navettas sub le commando de incaute capitanos.

THE INTERACTING EFFECTS OF PUBLIC HEALTH, FERTILITY BEHAVIOR AND GENERAL ECONOMY ON STANDARDS OF LIVING
II. QUALITATIVE EVALUATION OF FACTORS RESPONSIBLE FOR CONDITIONS IN COUNTRIES WITH SIMILAR SITUATIONS

By Alexander Langer, M.D.

and

Paul S. Henshaw, Ph.D.*

In the first paper of this series[1], a country Situation Index was developed, by means of which it was possible to classify countries and territories according to existent conditions of living. For this work, use was made of recently obtained *basic* data or indices for birth rates (B), death rates (D), population increase rates (P), population density (N), and *per capita* caloric intake (C), industrial energy consumed (E) and income (I), also, of *calculated* indices for total fertility ($2^P + 2^D$), population pressure $N(2^P + 2^D)$, and degree of economic development (CEI). The formula $\frac{CEI}{N(2^P + 2^D)}$, then, was used to obtain over-all Situation Index values.

It is the purpose of this paper to consider the relative importance of component determinants of level of living, especially total fertility, population pressure and economic development, and in so doing to recognize the particular role of public health undertakings and to identify countries that have similar conditions and problems.

In accomplishing these objectives, special procedures have been used, which for the most part, are qualitative in character. More quantitative considerations are left for later handling. In Table 1 of the first paper, numerical values were presented for the different indices, that is for each kind of basic data and for the calculated results. The various values given could of course be compared directly for the different regions and impressions gained thereby of similarities and differences, but the general picture becomes more comprehensible when various ranges of values are compared. Accordingly, each set of values was divided into five equal parts (except for extremes) and arbitrarily assigned classification *range numbers* (1 through 5) in sequential order (Table 1, this paper). To illustrate, birth rates for most countries are in the general range 0 to 5% per year. It was decided then to assign range number 1 to birth rates of 2% or below, range number 2 to those between 2 and 2.75, and so on, giving range number 5 to birth rates of 4.25 or above. The table shows range number assignments as made for each series of index values.

Range numbers, besides being more convenient, have certain meaning which is significant and which is of importance to objectives of this paper. Taking birth rates again as an example, lower range numbers are associated with lower birth rate values and higher range numbers with higher values. Accordingly, in terms of changing needs for commodities and resource mater-

*National Committee on Maternal Health, Inc., 2 East 103rd Street, New York 29, New York.

ials, it can be said that a more favorable situation exists when such values are high. In the table, each series of index values is shown in ascending or descending order in such a way as to correspond with more favorable situations when range numbers are low, and less favorable situations when they are high. Consistency of the arrangement should be apparent, with the possible exception of figures for death rates. At first, it might seem that the death rate sequence should be opposite to that for birth rates. As pointed out in the first paper, however, lower death rates coexist with higher levels of living, and higher death rates with the lower, thus causing the direction of sequence in each instance to have the same meaning.

Table 2 shows range numbers for the various indices for 70 countries and territories. Bearing in mind that the higher values indicate less favorable conditions, it is possible to see at a glance which countries have problems in nearly all of the categories and also which have similar or different problems. According to this analysis, it can be said, for example, that Egypt and Mauritius have problems in practically all categories, whereas Canada, as an example of the opposite extreme, has almost no problems. Proceeding from this generalized, and, for the most part, previously established information, further analysis was made by means of systematic arrangements.

Table 3 shows countries and territories with similar problems grouped together; that is, as indicated by the calculated indices. Since interest here centers mainly about the identification of elements or combinations of elements which interfere with achievement of higher levels of living, range numbers 3, 4 and 5 only have been shown, thus making the separation of *problem* and *no-problem* regions easier. Here it is pertinent to remember that range number 3 is intended in each case to represent intermediate or average conditions and values 4 and 5, less than average. Had range numbers 1 and 2 been included, they would appear in the spaces now left blank.

TABLE 1.—RANGE CLASSIFICATION NUMBERS IN RELATION TO DIFFERENT INDEX VALUES

Range No.	*B*	*D*	*P*	*N*	*C*	*E*	*I*	$\mathfrak{F}_P+\mathfrak{F}_D$	$N(\mathfrak{F}_P+\mathfrak{F}_D)$	*CEI*	$\frac{CEI}{N(\mathfrak{F}_P+\mathfrak{F}_D)}$
5	∞	∞	∞	∞	0	0	0	∞	∞	0	0
	4.25	1.80	3.00	210	2.05	0.25	125	8.00	800	110	0.1
4	3.50	1.50	2.25	150	2.40	0.75	250	6.50	600	330	1
3	2.75	1.20	1.50	90	2.75	1.25	375	5.00	400	1000	10
2	2.00	0.90	0.75	30	3.10	1.75	500	3.50	200	3000	100
1	0	0	0	0	∞	∞	∞	0	0	∞	∞

Explanation of symbols and expressions (as given in Paper 1): B, crude annual birth rates in %; D, crude annual death rates in %; P, natural increase rate (B—D); crude annual increase in %; N, inhabitants per km²; C, daily caloric intake per person (divided by 1000); E, industrial energy consumed per person per year (in tons coal equivalent); I, income per person per year (U.S. dollars); $\mathfrak{F}_P+\mathfrak{F}_D$, total fertility; $N(\mathfrak{F}_P+\mathfrak{F}_D)$, population pressure; CEI, economic development; $\frac{CEI}{N(\mathfrak{F}_P+\mathfrak{F}_D)}$, over-all Situation Index.

TABLE 2.—RANGE VALUES FOR DIFFERENT INDICES; 70 COUNTRIES

No. County	B	D	P	N	C	E	I	$2^p + 2^D$	$N(2^p + 2^D)$	CEI	$N(2^p + 2^D)$
										CEI	
1–Egypt	5	5	4	5	4	5	5	5	5	5	5
2–U. of S. Africa	3	1	3	1	3	2	3	3	1	2	2
3–Gold Coast	3	5	2	1	4	5	5	3	1	5	4
4–Mauritius	5	3	5	5	4	5	5	5	5	5	5
5–Canada	2	1	3	1	2	1	1	3	1	1	1
6–Costa Rica	5	2	5	1	3	4	5	5	2	5	4
7–Cuba	3	1	3	2	3	4	3	3	2	3	3
8–Dominican R.	4	2	5	2	5	5	5	5	3	5	5
9–El Salvador	5	4	5	2	4	5	5	5	4	5	5
10–Guatemala	5	5	5	1	5	5	5	5	2	5	5
11–Honduras	4	3	4	1	5	5	5	5	1	5	4
12–Mexico	5	3	4	1	5	4	5	5	1	4	3
13–Nicaragua	4	2	5	1	5	5	5	5	1	5	4
14–Panama	3	1	4	1	3	4	4	4	1	4	3
15–U.S.A.	2	2	2	1	1	1	1	2	1	1	1
16–Jamaica	3	2	3	3	5	5	5	4	5	5	5
17–Puerto Rico	4	2	4	5	5	4	4	5	5	4	5
18–Argentina	2	1	3	1	1	3	3	2	1	3	2
19–Bolivia	4	4	3	1	5	5	5	4	1	5	4
20–Brazil	4	5	4	1	4	4	5	5	1	5	3
21–Chile	3	3	3	1	4	3	4	4	1	3	3
22–Colombia	4	3	4	1	4	4	4	4	1	5	3
23–Ecuador	5	4	4	1	5	5	5	5	1	5	5
24–Paraguay	2	1	3	1	3	5	5	2	1	5	4
25–Peru	2	2	3	1	5	4	5	2	1	5	3
26–Uruguay	2	1	2	1	3	3	3	2	1	3	2
27–Venezuela	5	2	5	1	4	3	3	5	1	3	3
28–Burma	4	5	2	1	5	5	5	4	2	5	5
29–Ceylon	4	2	4	3	5	5	5	5	5	5	5
30–India	2	4	2	3	5	5	5	2	3	5	5
31–Indonesia	3	5	2	2	5	5	5	3	2	5	5
32–Iraq	3	1	3	1	5	5	5	2	1	5	4
33–Israel	3	1	4	2	3	3	3	4	3	3	3
34–Japan	2	2	3	5	4	3	5	2	5	4	4
35–Lebanon	2	1	3	3	3	5	5	2	4	5	4
36–Pakistan	1	3	1	2	5	5	5	2	2	5	5
37–Philippines	1	1	2	2	5	5	5	1	2	5	5
38–Syria	2	1	3	1	5	5	5	3	1	5	4
39–Thailand	3	2	3	2	5	5	5	3	2	5	5
40–Cyprus	2	1	3	2	3	4	5	3	2	5	4
41–F. of Malaya	5	3	5	2	5	4	5	5	3	5	5
42–Albania	3	3	3	2	3	4	5	3	2	5	4
43–Austria	1	2	1	2	3	2	4	1	2	3	3
44–Belgium	1	2	1	5	2	1	1	2	5	1	3
45–Bulgaria	2	3	2	2	2	4	4	2	2	4	4
46–Czechoslovakia	2	2	2	3	2	1	3	2	2	1	3
47–Denmark	1	1	2	3	1	2	1	2	2	1	2
48–Finland	2	2	2	1	2	2	3	2	1	2	2
49–France	1	3	1	2	2	1	2	2	2	1	3
50–Saar	1	2	2	5	2	1	1	2	5	1	3
51–W. Germany	1	2	1	4	3	1	3	1	4	2	3
52–Greece	2	2	3	2	3	4	4	2	2	5	4
53–Hungary	1	2	2	3	2	3	3	2	2	3	3
54–Iceland	2	1	3	1	1	1	2	3	1	1	1
55–Ireland	2	2	2	2	1	3	2	2	2	2	3
56–Italy	1	2	2	4	4	3	4	2	3	3	4
57–Luxembourg	1	2	1	3	2	1	1	1	3	1	3
58–Netherlands	2	1	3	5	2	2	1	2	5	1	3
59–Norway	1	1	2	1	1	1	1	2	1	1	1
60–Poland	3	2	3	2	3	1	3	3	3	2	3
61–Portugal	2	2	3	3	4	4	4	3	3	4	4
62–Roumania	1	5	1	2	3	4	4	2	2	4	4
63–Spain	2	2	2	2	3	4	4	2	2	3	3
64–Sweden	1	2	1	1	1	1	1	1	1	1	1
65–Switzerland	1	2	1	3	1	1	1	2	3	1	2
66–U. Kingdom	1	2	1	4	2	1	1	1	4	1	2
67–Yugoslavia	3	2	3	2	2	4	4	3	2	4	4
68–Australia	2	2	3	1	1	1	1	3	1	1	1
69–New Zealand	2	2	3	1	1	1	1	2	1	1	1
70–Hawaii	3	1	4	2	2	1	1	4	2	1	2

TABLE 3.—GROUPING OF COUNTRIES ACCORDING TO SIMILIARITY OF CONDITIONS

Group No.	*No.*	*Country*	$2P+2D$	$N(2P+2D)$	*CEI*	*CEI* $N(2P+2D)$
1	1	Egypt	5	5	5	5
	4	Mauritius	5	5	5	5
	29	Ceylon	5	5	5	5
	9	El Salvador	5	4	5	5
	16	Jamaica	4	5	5	5
	17	Puerto Rico	5	5	4	5
	8	Dominican R.	5	3	5	5
	41	F. of Malaya	5	3	5	5
	61	Portugal	3	3	4	4
	33	Israel	4	3	3	3
2	10	Guatemala	5		5	5
	31	Indonesia	3		5	5
	39	Thailand	3		5	5
	28	Burma	4		5	5
	6	Costa Rica	5		5	4
	11	Honduras	5		5	4
	13	Nicaragua	5		5	4
	23	Ecuador	5		5	5
	19	Bolivia	4		5	4
	38	Syria	3		5	4
	40	Cyprus	3		5	4
	42	Albania	3		5	4
	3	Gold Coast	3		5	4
	67	Yugoslavia	3		4	4
	20	Brazil	5		5	3
	12	Mexico	5		4	3
	22	Colombia	4		5	3
	27	Venezuela	5		3	3
	14	Panama	4		4	3
	21	Chile	4		3	3
	7	Cuba	3		3	3
3	30	India		3	5	5
	34	Japan		5	4	4
	35	Lebanon		4	5	4
	56	Italy		3	3	4
4	36	Pakistan			5	5
	37	Philippines			5	5
	24	Paraguay			5	4
	32	Iraq			5	4
	52	Greece			5	4
	45	Bulgaria			4	4
	62	Romania			4	4
	25	Peru			5	3
	43	Austria			3	3
	53	Hungary			3	3
	63	Spain			3	3
5	18	Argentina			3	
	26	Uruguay			3	
6	60	Poland	3	3		3
7	44	Belgium		5		3
	50	Saar		5		3
	58	Netherlands		5		3
	51	West Germany		4		3
	57	Luxembourg		3		3
8	46	Czechoslovakia				3
	49	France				3
	55	Ireland				3
9	70	Hawaii	4			
	2	U. of S. Africa	3			
	5	Canada	3			
	54	Iceland	3			
	68	Australia	3			
10	66	U. Kingdom		4		
	65	Switzerland		3		
11	15	U. S. A.				
	47	Denmark				
	48	Finland				
	59	Norway				
	64	Sweden				
	69	New Zealand				

In terms of total fertility, population pressure, and economic development, the various localities have been arranged in such a way as to show together those which have problems in all three categories (Group 1, Table 3), in two categories (Groups 2, 3 and 6), in one category (Groups 4, 5, 7, 9 and 10), and in no categories (Groups 8 and 11). In particular, they have been arranged so that all of the countries which have not achieved significant economic development (mainly industrialization) appear together (Groups 1 through 5).

At this point, it is necessary to keep clearly in mind what is meant by each of the calculated indices. Total fertility, as defined in Paper 1, refers not only to actual fertility but also to "wasted" fertility, meaning life capable of being saved by the types of public health programs being introduced so widely throughout the world; population pressure indicates the demand for available materials in terms of people in relation to land areas; and economic development specifies the degree of social, industrial and agricultural development. Finally, then, the over-all Situation Index shows the integration of total fertility, population pressure and economic development, yielding values useful for purposes of general comparison.

Taking the indices for economic development somewhat as a key or base point, the following are apparent: first, that approximately two-thirds of the regions listed are underdeveloped economically (Groups 1 through 5); second, that more than half of the regions have a high total fertility occurring concurrently with low economic development (Groups 1, 2, and 3); and third, that the regions which have high population pressure involve a variety of conditions: high fertility and low economic development (Group 1), high fertility and high economic development (Group 6), and low fertility and high economic development (Groups 7 and 10). Beyond this, similar groupings can be made of the more favorable conditions. Looking generally at the figures as arranged and as based on the derivations outlined, impressions can be gained of difficulties which must be overcome if further economic development is to be achieved. Certain regions, it is obvious, will be aided by low fertility and opportunity to expand, whereas others will at the same time have to compensate for high fertility or overcrowded conditions and, in some instances, both.

There is before us, therefore, a picture which not only identifies certain of the elements responsible for lower levels of living but at the same time indicates various combinations of the impediments which must be overcome if further advancements are to be made. In the tables, over-all Situation Index values have been included, thus permitting reference to the general situation as different components are examined. Usefulness of Table 3 in combination with Table 2 will be illustrated by taking specific examples.

The United States will be taken as an example of regions with uniformly favorable conditions (Group 11). By referring to Table 2, it is seen that while the birth, death and population increase rates (B, D and P) are not in the lowest range, they are nevertheless in the favorable range. It is seen also that population density (N) is low, indicating opportunity for expansion, and that the elements for economic development (C, E and I) are uniformly in the most favorable range. Turning then to the calculated indices, it is seen that total fertility is in the second best category, that population pressure is low due mainly to low density, and that the general figure for

economic development is favorable, since all of the component elements are favorable. This combination of conditions results in an over-all Situation Index in the top range.

Canada, representing Group 9, is similar to the United States except that total fertility is significantly higher. This condition, however, is well compensated by low population pressure and by the advanced economic development, resulting in an over-all Situation Index in the best range. Because of the opportunity to expand in Canada, it is apparent that increasing population, if it can be combined with high economic development, will in all probability contribute to an increasing level of living for some time to come.

Belgium is of interest as an example of Group 7. In this country, the unusually high economic development and associated low fertility are being opposed by high population pressure caused by high density, yielding a Situation Index value which is only intermediate. Because of lack of opportunity to expand, any increase in fertility in Belgium will of necessity have to be compensated by further economic development (mainly industrial), if level of living is not to deteriorate.

Considering next the economically underdeveloped regions, Egypt (Nile Valley) will be taken as a representative of Group 1. Here conditions of high birth, death and increase rates, high density and consequent high population pressure are going along together. These conditions, combined with low economic development in all categories, account for the least favorable over-all situation. Localities which fall in this category are of the type which have double handicaps so far as economic improvement is concerned. Not only must they overcome the low level living standards of existing populations but also they must provide adequately for rapid increases at the same time. More than this, since economic development usually carries with it improvements in conditions of health, improvements which often result in marked reduction of infant mortality and extension of life span, the problem is rendered even more difficult. There is question as to whether significant economic development in such instances can be accomplished without some lessening of birth rate going in advance or, at least, concurrently.

Problems of public health advancement, as part of economic improvement programs, also characterize the situation in the case of regions listed in Group 3, for which India will be considered as an example. Here, although the birth rate is not high, comparatively (India, 2.48; United States, 2.45—Paper 1), death rate is significantly higher (India, 1.60; United States, 0.96), resulting in a net increase which is comparatively quite low (India, 0.88; United States, 1.49). It is to be expected, therefore, that any improvement program which includes health measures will result almost immediately in an upsurge in population increase due to reduction of the high death rate. Accordingly, since the low degree of economic development in India, combined with a fairly high density, results in difficulty to absorb the existing low level of population increase, any improvement program which does not deal with population growth mechanisms may be found to result in an offsetting of economic gains, if not in an actual worsening of level of living.

Conditions in Guatemala will be taken as representative of countries which have room for expansion (that is, which have low density) but which are yet underdeveloped economically (Group 2). In this instance, low eco-

nomic development and high fertility are occurring together. This is a situation not favorable for taking advantage of the opportunity to expand since so much of the available manpower must be utilized in maintenance of mere subsistance or of the *status quo*. It is in situations of this type that assistance from the outside is often so very effective.

There remains Group 4 to be considered, and Greece will be taken as the example. In this country, neither fertility nor population pressure are excessive, but despite these circumstances significant economic development has not been achieved. It would appear that Greece is not greatly unlike Guatemala in that nearly all of the available energy is consumed in maintaining existing conditions.

A method has thus been presented for obtaining information, mainly qualitative, about significant determinants of level of living. It is to be emphasized, however, that analyses making use of the method cannot be more reliable than the basic data nor the underlying assumptions used. Employment of the method should in all cases be preceded by careful consideration of the accuracy of data and of the assumptions as they apply to the period of time under consideration. Impressions gained by the studies here resemble those sometimes developed by *a priori* reasoning, but they have the advantage of being based on figures for actual conditions of various types which have been set forth systematically according to operating principles believed to apply.

Summary. On the basis of selected range numbers for applicable indices, groupings of countries and territories with similar conditions of different types were developed. By means of these, it was possible to identify component determinants in various combinations which act to stimulate or impede economic development. Situations were recognized in which public health undertakings may be expected to retard improvements in level of living as well as benefit them. Findings show the inadequacy of characterizing any region or locality by dealing with a single determiner and the importance of employing a comprehensive approach, such as the over-all Situation Index, if reliable impressions are to be obtained.

REFERENCE

1. **Langer, A.,** and **Henshaw, P. S.:** Am. J. Med. Sci., **230**, 119, 1955.

CORRECTION: A calculation error sufficiently large to cause confusion has occurred in connection with the Situation Index for Ecuador (Table 1, Paper 1, of this Series). The value should be 0.07.

(Interlingua on page 519)

AN EXPERIMENTAL STUDY OF THE TOXICITY OF FERROUS GLUCONATE

By James O. Hoppe, Ph.D.
MEMBER

G. Marie Agnew Marcelli, M.S.
RESEARCH ASSOCIATE

AND

Maurice L. Tainter, M.D.
DIRECTOR

(From the Sterling-Winthrop Research Institute, Rensselaer, New York)

From an extensive survey of the pharmacological and clinical literature on the toxicity of iron[3] it appeared that ferrous gluconate was less dangerous in overdoses than the other popular iron salts. No cases of poisoning from this iron salt have appeared in the literature, in contrast to the numerous ones with other iron compounds, and particularly with ferrous sulfate. Few pharmacologic data have been published on ferrous gluconate. Therefore, it was decided to carry out a series of studies in our laboratories which would explore and more accurately define this apparent lower experimental and clinical toxicity. Observations on the systemic and local toxicity of ferrous sulfate were included for comparison with the ferrous gluconate results.

Methods. The acute toxicity of ferrous gluconate was determined in direct comparison with that of ferrous sulfate following both intravenous and oral administration in male, albino Swiss mice weighing 22 ± 2 gm. For the intravenous injection, the compounds were administered in aqueous solution in a volume of 0.01 cc./gm. of body weight at a rate of 1.0 cc./minute. A volume of 0.01 cc./gm. of body weight also was used for oral administration. In addition, the acute toxicity of ferrous gluconate was compared with that of ferrous sulfate following oral administration in male, Sprague-Dawley rats weighing 100 ± 10 gms. The compounds in aqueous solution were administered orally in a volume of 1.0 cc./100 gm. of body weight. The mice and rats were observed closely for several hours following injection, and the LD_{50} ± its standard error was estimated at the end of 24 hours by the method of Miller and Tainter[4]. The animals were held under close observation for a period of one week following injection and any delayed manifestations of toxicity were recorded. Where delayed deaths occurred after 24 hours, the LD_{50} was recalculated at the end of the 7-day observation period. Ferrous gluconate and ferrous sulfate were administered orally as a finely divided powder by capsule to cats, weighing 2 to 3 kg., and to mongrel dogs, weighing 7 to 12 kg., in an effort to determine the acute lethal dose following oral administration. After failing to produce fatalities by oral administration of large single doses of either compound, an effort was made to determine whether death occurred following repeated medication with massive oral dosages. Daily doses of 25, 50, 100, 200 and 400 mg./kg. of ferrous sulfate and 100, 200, 400, 800 and 1600 mg./kg. of ferrous gluconate were administered as a powder by capsule to two cats at each dose level 5 days a week for 2 weeks. The cats were observed closely following each medication for evidence of systemic intoxication and the body weights were recorded 3 times a week. All animals were housed in air-conditioned quarters with food and water available at all times, with the exception of the period immediately preceding the oral medications. The mice and rats were fasted for 4 hours and the cats and dogs for 18 hours before oral administration of the ferrous gluconate and ferrous sulfate dosages.

Local tissue toxicity was estimated by means of the trypan blue irritation test procedure[2]. Saline or aqueous-saline solutions of ferrous gluconate from 1% to 8% and ferrous sulfate from 0.25% to 2%, were injected intracutaneously into the abdominal skin of the rabbit followed by the intravenous injection of 10 mg./kg. of trypan blue. The results are expressed in terms of the Threshold Irritant Concentration (TIC) or that concentration, in per cent, which produces no more than a mild irritation (a faint but discernible blue color at the site of injection).

Ferrous gluconate* and ferrous sulfate, U.S.P., were administered as the salt in each case. The results have been calculated in terms of iron in order to provide a more direct comparison of the toxicity values. Percentage factors used for these calculations were as follows:

Ferrous sulfate .7 H_2O = 20.09% iron
Ferrous gluconate .2 H_2O = 11.58% iron

1. ACUTE TOXICITY STUDIES IN THE MOUSE. a. *Intravenous.* As shown in Table 1, ferrous sulfate was found to be approximately twice as toxic as ferrous gluconate in terms of the salt. When the data were calculated in terms of ferrous iron, there did not appear to be any apparent difference in the acute intravenous toxicity of these two compounds in mice. The value of 13 ± 1 mg./kg. for ferrous sulfate is in almost precise agreement with the value, 13.8 mg./kg. of iron, reported for ferrous sulfate in mice by Edge and Somers[1].

Although a majority of the mice died in the first 24 hours following injection, several deaths occurred in the next 3 to 5 days. No deaths occurred after 5 days. The LD_{50} value for ferrous gluconate at 7 days was not significantly different from the 24-hour value. The 7-day LD_{50} value for ferrous sulfate, however, indicated a significant increase in toxicity due to delayed deaths. In the acute deaths, the mice were severely depressed and lapsed into complete prostration which terminated in a brief clonic convulsive episode with cessation of respiration preceding cardiac arrest. A majority of the acute deaths occurred in one to five minutes after intravenous injection.

b. *Oral.* The acute oral toxicity data in Table 1 show that ferrous gluconate is significantly less toxic than ferrous sulfate, both in terms of the salt and of ferrous iron. The oral LD_{50} for ferrous sulfate was found to be 1520 mg./kg. compared with 3700 mg./kg. of ferrous gluconate which, when expressed in terms of ferrous iron, amounts to 306 mg./kg. as the sulfate and 429 mg./kg. as the gluconate. These differences are statistically significant and indicate that the gluconate, in terms of ferrous iron content, is approximately 40% better tolerated than the sulfate. There were no delayed deaths with either compound following oral administration in mice.

2. ACUTE ORAL TOXICITY STUDIES IN THE RAT. The acute oral toxicity data

TABLE 1.—ACUTE TOXICITY OF FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) VERSUS FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) IN MICE

			LD_{50} ± s.e. mg./kg.			
			As Salt		*As Fe^{++}*	
Compound	*Route of Adminis.*	*No. of Animals*	*24 Hours*	*7 Days*	*24 Hours*	*7 Days*
Ferrous sulfate	I.V.	30	65 ± 4.8	51 ± 4.6	13 ± 1	10.2 ± 0.9
Ferrous gluconate	I.V.	40	114 ± 7.6	98 ± 6.8	12.5 ± 0.7	10.8 ± 0.7
Ferrous sulfate	Oral	30	1520 ± 130	1520 ± 130	306 ± 26	306 ± 26
Ferrous gluconate	Oral	60	3700 ± 145	3700 ± 145	429 ± 17	429 ± 17

*Ferrous gluconate was used in the form of Fergon, supplied by Winthrop-Stearns Inc.

in the rat were found to be of a similar order of magnitude as those found in the mouse as will be noted from the data in Table 2. In terms of the salts, ferrous gluconate was found to be approximately one-third as toxic as ferrous sulfate following oral administration in the rat. When compared in terms of ferrous iron, ferrous gluconate is significantly less toxic, being approximately one-half as toxic as ferrous sulfate. No delayed deaths were observed with ferrous sulfate; one delayed death was observed with ferrous gluconate.

3. ACUTE ORAL TOXICITY IN THE CAT. It was not possible to obtain mortality data by this route of administration at the dose levels employed, since emesis occurred in every cat within 15 minutes to one hour after medication. Severe diarrhea also was observed but became less evident at the higher dosages as the promptness and intensity of emesis increased. It was concluded from these experiments that the acute oral lethal dose of ferrous sulfate in cats was more than 200 mg./kg. and more than 400 mg./kg. for ferrous gluconate.

The pattern of emesis was sufficiently prominent and consistent to permit the estimation of the approximate median emetic dose, AED_{50}, (the approximate dose producing emesis in 50% of the cats) as a criterion for comparing the gastric tolerance to these two compounds in cats. A summary of the emetic effects and of the incidence of diarrhea is given in Table 3. It will be noted that the dose of ferrous gluconate required to produce emesis in 50% of the cats was more than three times as large as that of ferrous sulfate. About twice as much iron in the form of ferrous gluconate was tolerated without vomiting as was tolerated in the form of the sulfate.

4. ACUTE ORAL TOXICITY STUDIES IN THE DOG. Six dogs, one at each dosage level, were given capsules of finely divided ferrous gluconate in amounts ranging from 100 to 3200 mg./kg. Five other

TABLE 2.—ACUTE ORAL TOXICITY OF FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) AND FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) IN RATS

		$LD_{50} \pm s.e.$ mg./kg.			
		As Salt		*As Fe^{++}*	
Compound	*No. of Animals*	*24 Hours*	*7 Days*	*24 Hours*	*7 Days*
Ferrous sulfate	30	1480 ± 184	1480 ± 184	298 ± 37	298 ± 37
Ferrous gluconate	30	4600 ± 560	4500 ± 400	518 ± 63	507 ± 45

TABLE 3.—EFFECTS OF SINGLE ORAL DOSAGES OF FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) AND FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) IN CATS

		Emetic Effects			*Diarrhea*
		No. Vomited	*AED_{50}, mg./kg.*		*No. Showing Diar.*
Compound	*Dose mg./kg.*	*No. Medicated*	*As Salt*	*As Fe^{++}*	*No. Medicated*
Ferrous sulfate	25	1/4	82	16	2/4
	50	2/4	..	..	2/4
	100	1/4	..	..	0/4
	200	4/4	..	..	0/4
Ferrous gluconate	100	0/4	267	31	2/4
	200	1/4	..	..	1/4
	400	4/4	..	..	0/4

dogs received similar capsules of ferrous sulfate in doses from 50 to 800 mg./kg. No deaths or serious evidence of acute systemic intoxication were observed in the dogs at doses up to and including the highest dose level, 800 mg./kg. of ferrous sulfate or 3200 mg./kg. of ferrous gluconate. The most obvious effects produced by these two compounds were emesis and diarrhea (Table 4). Vomiting was noted in the dog receiving 50 mg./kg. of ferrous sulfate but was not encountered in the others until the dose was raised to 800 mg./kg., when a prompt and vigorous emetic reaction was observed. With ferrous gluconate, vomiting did not occur until doses of 1600 and 3200 mg./kg. were reached. A watery diarrhea became apparent approximately one hour after oral administration of 100 mg./kg. of ferrous sulfate and 800 mg./kg. of ferrous gluconate. At doses of 200 and 400 mg./kg. of ferrous gluconate, diarrhea developed the morning of the day following medication.

The occurrence of vomiting and diarrhea, indicative of a protective mechanism similar to that observed in the cat, interfered with the attempt to estimate the acute oral lethal dosage of these compounds in dogs.

5. REPEATED ORAL MEDICATION IN THE CAT. Since it had not been possible to obtain mortality following oral administration of large single doses of either compound in the cat, an effort was made to determine whether death would result from repeated medication with massive hypertherapeutic doses. Daily doses of 25, 50, 100, 200 and 400 mg./kg. of ferrous sulfate and 100, 200, 400, 800 and 1600 mg./kg. of ferrous gluconate were administered as a powder by capsule to 2 cats at each dose level 5 days a week for 2 weeks. No serious body weight changes or mortality occurred among the cats receiving ferrous gluconate. However, one cat on 400 mg./kg. of ferrous sulfate died following the fifth dose. Some impairment of appetite occurred in the second cat at this dose level, but no serious loss in weight occurred and the cat survived the full medication schedule. Occasional vomiting and diarrhea occurred at the lower dosages with both compounds as noted in Table 5. The intensity of the emesis increased with increase of dosage and was associated with a decrease in the incidence of diarrhea. The emesis appeared to be entirely local in effect, since it occurred in less than an hour after medication. Other than the emesis, the cats appeared to suffer no ill effects from the medication. The appetite except at the highest dosages remained normal in every cat.

6. TISSUE IRRITATION STUDIES. Because of the apparent difference in incidence of gastrointestinal irritation observed with these two compounds in cats and dogs, a comparison of their irritant properties was made by means of the trypan blue irritation test[2] with results as summarized in Table 6.

Ferrous gluconate was observed to be distinctly less irritant than ferrous sulfate. The relative irritancy of these two compounds was similar to that observed in the acute oral studies in cats. The TIC (threshold irritation concentration) for ferrous sulfate was found to be 0.25% and for ferrous gluconate four times larger or 1.0%. Recalculation of these data in terms of ferrous iron indicates that the local tissue irritation of ferrous gluconate is less than one-half that of ferrous sulfate. The evidence of a lower local tissue toxicity with ferrous gluconate correlates well with the finding that the acute oral toxicity of ferrous gluconate is significantly less than that of ferrous sulfate upon oral administration to the mouse and rat. In addition, these laboratory results confirm the clinical observations that

ferrous gluconate, being less irritating, is much better tolerated than ferrous sulfate.

Discussion. Comparison of the present acute toxicity data on ferrous gluconate and ferrous sulfate with the data available in the literature indicates some agreement and also some wide discrepancies. The present acute oral LD_{50} values of 1520 ± 130 mg./kg. for ferrous sulfate ($FeSO_4 \cdot 7H_2O$) and 3700 ± 145 mg./kg. for ferrous gluconate ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) in the mouse indicate a higher acute oral toxicity for these substances than that reported for the mouse in the literature.

TABLE 4.—EFFECTS OF SINGLE ORAL DOSAGES OF FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) AND FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) IN DOGS

Compound	*Dose, mg./kg.*		*Vomiting*	*Diarrhea*
	As Salt	*As Fe^{++}*		
Ferrous sulfate	50	10.0	Yes	No
	100	20.1	No	Yes at 2 hours
	200	40.2	No	Yes at 1 hour
	400	80.4	No	Yes at 1 hour
	800	160.8	Yes at 10 min.	Yes at 1½ hours
Ferrous gluconate	100	11.6	No	No
	200	23.2	No	Yes at 24 hours
	400	46.4	No	Yes at 24 hours
	800	92.8	No	Yes at 1½ hours
	1600	185.6	Yes at 1 hour	Yes at 2 hours
	3200	371.2	Yes at 1½ hours	Yes at 1 hour

TABLE 5.—EFFECTS OF REPEATED MASSIVE ORAL DOSAGE (5 DAYS A WEEK FOR 2 WEEKS) OF FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) AND FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) IN CATS

Compound	*Dose, mg./kg.*		*Mortality*	*Emetic Effects*	*Diarrhea*
	As Salt	*As Fe^{++}*			
Ferrous sulfate	25	5.0	0/2	Occasional, one cat	None
	50	10.0	0/2	Occasional, one cat	Occasional, both cats
	100	20.1	0/2	Frequent, both cats	Occasional, both cats
	200	40.2	0/2	Frequent, both cats	Frequent, both cats
	400	80.4	1/2 (7th day)	Daily	None
Ferrous gluconate	100	11.6	0/2	Occasional, one cat	Occasional, one cat
	200	23.2	0/2	Occasional, both cats	Frequent, both cats
	400	46.4	0/2	Frequent, both cats	Occasional, both cats
	800	92.8	0/2	Frequent, both cats	Occasional, both cats
	1600	185.6	0/2	Daily	Occasional, both cats

TABLE 6.—TRYPAN BLUE IRRITATION DATA ON FERROUS SULFATE ($FeSO_4 \cdot 7H_2O$) VERSUS FERROUS GLUCONATE ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$)

Compound	*Concentration in Per Cent (as salt)*	*Maximum Av. Irritation Score*	*Adjective Rating*	**TIC, %*	
				Salt	*Fe^{++}*
Ferrous sulfate	0.25	1.3	Mild	0.25	0.05
	0.5	7.3	Moderate		
	1.0	16.0	Marked		
	2.0	16.0	Marked		
Ferrous gluconate	1.0	3.3	Mild	1.0	0.12
	2.0	5.3	Moderate		
	4.0	13.3	Marked		
	8.0	16.0	Marked		

*TIC—Threshold irritant concentration.

These variations may be due to differences in methods of administration, strain of mice, conditions of assay, and the like. The acute intravenous toxicity for ferrous sulfate as ferrous iron, 13 ± 1 mg./kg., however, agrees almost precisely with the reported literature value of 13.8 mg./kg.[1] In the case of the cat, a literature value of greater than 500 mg./kg. of ferrous sulfate was reported. In the present study, no mortality was observed with single oral doses of ferrous sulfate up to and including 200 mg./kg. When given by repeated oral administration, however, one of two cats died at the end of the first week at a dose of 400 mg./kg. of ferrous sulfate. An estimated acute oral lethal dose of 800 mg./kg. of ferrous sulfate for the dog has been reported[5]. In the present study no mortality was observed following oral administration of ferrous sulfate at dosages up to and including 800 mg./kg. in the dog. Copious vomiting was encountered in both the cat and the dog, which tended to interfere with attempts to estimate the acute oral lethal dose of ferrous sulfate in these two species.

The fact that copious and effective emesis interfered with the estimation of the acute oral lethal dose of ferrous sulfate in both the cat and dog indicates that this protective mechanism may be better developed in these two species than it is in the human. It is of interest to note that the estimated oral median lethal dose of 900 mg./kg. for ferrous sulfate in children, referred to earlier[3], is within the limits of experimental error for the acute oral LD_{50} values for ferrous sulfate in the mouse (1520 ± 130 mg./kg.) and the rat (1480 ± 184 mg./kg.) as established in the present investigation.

Summary. The results of a direct comparison of the acute systemic and local toxicity of ferrous sulfate ($FeSO_4 \cdot 7H_2O$) and ferrous gluconate ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) in experimental animals may be summarized as follows:

1. Studies in mice indicate that the acute intravenous toxicity of ferrous gluconate (114 ± 7.6 mg./kg.) is approximately half that of ferrous sulfate (65 ± 4.8 mg./kg.) in terms of absolute weights of the salts. In terms of iron, however, there is no apparent difference in the toxicity of the two compounds by this route of administration. Delayed deaths occurred with both compounds but were significantly greater with ferrous sulfate.

2. Lower toxicity was observed with both compounds when given orally to mice. The acute oral toxicity values (ferrous sulfate, 1520 ± 130 mg./kg.; ferrous gluconate, 3700 ± 145 mg./kg.) were more than twenty times as large as those following acute intravenous injection. In the rat ferrous gluconate (4600 ± 560 mg./kg.) was only one-third as toxic as ferrous sulfate (1480 ± 184 mg./kg.) as the salt and one-half as toxic in terms of ferrous iron. No delayed deaths of significance were observed following oral administration in either species.

3. Attempts to estimate the acute oral toxicity in cats were unsuccessful, due to intense local gastric irritation which resulted in prompt and copious vomiting. Approximately twice as much ferrous iron in the form of ferrous gluconate as ferrous sulfate was tolerated before vomiting occurred.

4. In the dog the acute oral median lethal dose was estimated to be greater than 800 mg./kg. of ferrous sulfate and more than 3200 mg./kg. of ferrous gluconate. No deaths or serious evidence of acute systemic intoxication were observed at these doses. The emesis and diarrhea produced by both compounds rendered attempts to estimate accurate LD_{50} values impracticable.

5. Local tissue irritation studies indicated that twice as much iron in the

form of ferrous gluconate could be intracutaneously injected without serious damage as could be tolerated in the form of the sulfate.

6. Daily oral administration of ferrous gluconate powder by capsule to cats, 5 days a week for 2 weeks at the hypertherapeutic dosages of 100 to 1600 mg./kg. produced no mortality and no evidence of cumulative toxicity. Emesis and diarrhea were noted at all dose levels. Emesis was particularly prompt and copious at the highest dose levels.

7. Similar daily oral administration of ferrous sulfate to cats at doses of 25 to 400 mg./kg. resulted in death of one of two cats at the 400 mg. level at the end of the first week. Other than emesis and diarrhea, no additional serious toxic effects were noted. No cumulative toxic effects were observed.

8. The magnitude of the acute oral toxicity values when compared with the acute intravenous figures in mice indicates a relatively low order of absorption from the intestinal tract. An additional safety factor is evident from the oral studies in the cat and the dog in which the local irritant effects induce a protective emesis. These data suggest prompt, gentle gastric lavage along with supportive therapy for shock as an effective emergency measure in those cases where, for any reason, vomiting does not occur spontaneously following oral ingestion of ferrus sulfate, ferrous gluconate or other soluble iron salts.

9. These studies clearly establish that ferrous gluconate is less irritating and less toxic than ferrous sulfate when considered from the standpoint of the total weight of drug administered or in terms of their iron contents. A firm experimental basis for the lack of clinical toxicity and for the therapeutic preference for ferrous gluconate, therefore, appears to be demonstrable.

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SUMMARIO IN INTERLINGUA

Un Studio Experimental del Toxicitate de Gluconato Ferrose

Le sequente es un summario del resultatos de un comparation directe del acute toxicitate systemic e local de sulfato ferrose ($FeSO_4 \cdot 7H_2O$) e gluconato ferrose ($Fe[C_6H_{11}O_7]_2 \cdot 2H_2O$) in animales experimental:

1. Studios in muses indica que le acute toxicitate intravenose de gluconato ferrose (114 ± 7,6 mg/kg) es approximativemente un medietate del acute toxicitate intravenose de sulfato ferrose (65 ± 4,8 mg/kg), super le base del pesos absolute del sales. Super le base del contento de ferro, del altere latere, il ha nulle apparente differentia in le toxicitate del duo compositos in administrationes intravenose. Mortes retardate occurreva con ambe compositos, sed illos esseva significativemente plus numerose con sulfato ferrose.

2. Pro ambe compositos, un plus basse toxicitate esseva observate in muses quando le administration esseva effectuate per le via oral. Le pesos de acute toxicitate oral (sulfato ferrose, 1520 ± 130 mg/kg; gluconato ferrose, 3700 ± 145 mg/kg) esseva plus que 20 vices plus grande que illos del acute toxicitate intravenose. In rattos le toxicitate de gluconato ferrose (4600 ± 560 mg/kg) esseva solmente un tertio del toxicitate de sulfato ferrose (1480 ± 184 mg/kg), super le base del pesos absolute del sales, e un medietate, super le base del ferro ferrose. Mortes retardate non esseva observate in numeros significative post le administration oal in o le muses o le rattos.

3. Nos non succedeva a estimar le acute toxicitate oral del duo compositos in experimentos con cattos proque iste animales reageva per un intense irritation gastric local que resultava in un prompte e copiose vomito. Circa duo vices el quantitate de ferro ferrose esseva tolerate in le forma de gluconato ferrose que in le forma de sulfato ferrose ante que le vomito occurreva.

4. In canes le peso median del acute dose mortal in administrationes oral esseva estimate como supra 800 mg/kg de sulfato ferrose e supra 3200 mg/kg de gluconato ferrose. Con iste doses nulle mortes o serie signos de acute intoxication systemic esseva observate. Le emesis e le diarrhea producite per ambe compositos non permitteva le determination de exacte valores.

5. Studios de histo-irritation local indicava que duo vices le quantitate de ferro in le forma de gluconato ferrose que in le forma de sulfato ferrose poteva esser injicite intracutaneemente sin resultante damnos seriose.

6. Le diurne administration oral de pulvere de gluconato ferrose in capsulas; 5 dies per septimana, durante 2 septimanas, in doses hypertherapeutic de inter 100 e 1600 mg/kg; non produceva ulle mortalitate in cattos. In iste experimentos nulle prova de toxicitate cumulative esseva observate. Emesis e diarrhea esseva notate con omne nivellos de dosage. Al plus alte nivellos, emesis esseva specialmente prompte e copiose.

7. In simile experimentos con cattos, diurne administrationes oral de sulfato ferrose in doses de inter 25 e 400 mg/kg resultava in le morte de un ex duo cattos al fin del prime septimana de administrationes al nivello de 400 mg/kg. Foras del emesis e del diarrhea nulle altere serie effectos esseva notate. Nulle toxicitate cumulative esseva observate.

8. Le magnitude del valores de acute toxicitate oral in muses comparate con le magnitude del valores de acute toxicitate intravenose indica un relativemente basse grado de absorption ab le tubo intestinal. Un factor de securitate additional es evidente ab le studios oral in cattos e canes in que le irritante effectos local induce un emesis protective. Iste datos suggere un prompte e dulce lavage gastric insimul con therapia supportative pro choc como un efficace prime mesura in casos in que pro un o altere ration emesis non occurre spontaneemente post ingestion oral de sulfato ferrose, gluconato ferrose, o alicun altere solubile sal de ferro.

9. Iste studios establi clarmente le facto que gluconato ferrose es minus irritante e minus toxic que sulfato ferrose, considerate tanto ab le puncto de vista del peso total del droga administrate como etiam ab le puncto de vista del contento de ferro. Assi il pare possibile demonstrar un firme base experimental pro le absentia de toxicitate clinic de gluconato ferrose e pro su preferibilitate therapeutic.

CRYOGLOBULINEMIA ASSOCIATED WITH GANGRENE OF THE DIGITS

By Ralph M. Myerson, M.D.

and

Robert E. Stout, M.D.

(From the Medical Service, Veterans Administration Hospital, Philadelphia, Pennsylvania)

The occurrence of cold precipitable serum proteins, termed cryoglobulins by Lerner and Watson[22], is not rare. Their presence has been noted in a variety of clinical conditions, chiefly multiple myeloma, chronic lymphatic leukemia, kala azar, malaria, rheumatoid arthritis and subacute bacterial endocarditis[2-5,8,9,11,21,27,35]. Cryoglobulinemia has also been described in cirrhosis of the liver, hepatitis, pneumonia, tuberculosis, bronchiectasis, asthma, coronary artery disease, rheumatic heart disease, chronic glomerulonephritis, polyarteritis nodosa, disseminated lupus erythematosus, thromboembolic pulmonary vascular sclerosis, gout and brucellosis[1,2,8,12,18,20,21,28,31].

Occasionally, cryoglobulinemia has been associated with a syndrome characterized by cold sensitivity, purpura and Raynaud's phenomena. It has been inferred that cryoglobulins produce this clinical picture by causing stasis and sludging of blood with subsequent injury to the involved areas[2,22,25,33,36]. This theory is substantiated by the observance of this process in retinal vessels and by the postmortem demonstration of intravascular gelatinous material[2,6,7,25,28].

Cugudda[7] and Hutchinson and Howell[17] have described gangrene of the extremities associated with the presence of cryoglobulins in the blood. The discovery of 3 similar cases within a period of one year has lead us to believe that this association is more common than previously reported.

Report of Cases. CASE 1. H. S., a 33-year-old Negro male, was admitted to the Veterans Administration Hospital, Philadelphia, on March 3, 1954, because of progressive dyspnea, orthopnea and ankle edema of 6 months' duration.

In 1943, a routine serological test for syphilis was reported positive and the patient was treated with an arsenical and bismuth. Because of subsequent positive serological tests, he had received several courses of penicillin.

In 1945, the patient developed migratory polyarthritis and fever, associated with electrocardiographic changes, and he was hospitalized for 3 months for acute rheumatic fever.

Sensitivity of the hands to cold began in 1946 and during the next year ulceration and gangrenous changes developed on the tips of all of his fingers. Bilateral cervical sympathectomy was performed in 1947. At this time mitral systolic and diastolic murmurs were noted and the patient was found to have hypertension.

Cold sensitivity continued following the sympathectomies. Between 1947 and 1950 he experienced recurrent episodes of polyarthritis, fever and dyspnea, and he had been on a regimen of digitalis and salt restriction since 1950. Skin and muscle biopsies were reported as normal in 1953. Digitalis was discontinued 6 months prior to admission and during this period, the patient developed the signs and symptoms of progressive cardiac decompensation.

Physical examination on admission revealed an acutely ill Negro man in respiratory distress. Temperature was 98.0° F.; pulse 100 per min.; respirations 26 per min.; blood pressure 170 systolic, 140 diastolic. Fundoscopic examination revealed Grade II hypertensive changes. Several small "red spots" were scattered throughout both retinae. These were interpreted as microaneurysms or deep hemorrhages. The neck veins were distended and rales were present over the lower half of both lung fields. The heart was en-

larged to the left; the rhythm was regular, and systolic and diastolic murmurs were heard at the apex. The liver was felt 3 cm. below the right costal margin and was slightly tender. Moderate edema of the feet and ankles was present. The skin of the fingers of both hands was shiny and atrophic and flexion deformities of all fingers were present. The tips of several fingers of both hands were ulcerated.

The initial impression was generalized scleroderma. The patient was treated with digitalis, salt restriction and diuretics with rapid improvement. Laboratory studies revealed a leukocyte count of 7900 per c.mm. with a normal differential count, a hemoglobin of 12.5 gm., a hematocrit of 40% and a sedimentation rate of 33 mm. per hr. Urinalyses were normal except for slight albuminuria. There was no Bence Jones proteinuria. Tests of renal and hepatic function were within normal limits. Blood urea nitrogen, blood glucose, serum chlorides, sodium, potassium and CO_2 combining power were normal. L. E. cell preparations, bone marrow aspiration and cold agglutinations were negative. Electrocardiograms revealed notched P waves and left ventricular strain. Chest roentgenograms revealed generalized cardiac enlargement. Roentgenograms of the skeletal system revealed beginning destruction and sharpening of the tufts of the terminal phalanges of all fingers. A gastrointestinal series was interpreted as showing hypoperistalsis of the esophagus suggesting scleroderma. An intravenous urogram was within normal limits.

Serum protein determinations and electrophoretic fractionations are shown in Table 1. The total protein varied between 9.4 and 10.0 gm. per 100 cc., with albumin of 3.5 to 3.7 gm. and globulin of 5.7 to 6.5 gm. When the serum was cooled to 4° C. for 48 to 72 hours a dense gel formed. Warming immediately dispersed the gel. The difference between serum protein determinations performed at 37° C. and those determined after centrifugation and separation of the cold precipitable proteins averaged about 1 gm. This was thought to represent the amount of cryoglobulins present.

The patient was discharged on a program of maintenance digitalis, diuretics and low salt diet.

He was readmitted to the hospital on October 17, 1954, because of the sudden onset of disorientation, hallucinations and maniacal behavior. Physical findings were essentially unchanged from those at the time of his previous discharge from the hospital. There were no abnormal neurological findings. Laboratory findings were the same as on his previous admission. The patient responded slowly to sedation and supportive therapy. No definite cause for his abnormal behavior could be found. He was discharged on November 5, 1954.

On March 20, 1955 the patient noticed the sudden onset of blindness in the right eye. An ophthalmological consultant diagnosed occlusion of the central retinal artery. Cryoglobulinemia was still present.

TABLE 1.—SERUM PROTEIN FRACTIONATION OF 3 PATIENTS EXHIBITING CRYOGLOBULINEMIA ASSOCIATED WITH GANGRENE OF THE DIGITS

	Normal Average *Gm.%*	*H.S.* *Gm.%*	*W.W.* *Gm.%*	*C.M.* *Gm.%*
Total Protein	6.90	9.40	7.90	7.70
Albumin	4.00	3.26	3.32	3.43
Globulin	2.90	6.14	4.58	4.27
Alpha[1] Globulin	0.30	0.60	0.49	0.39
Alpha[2] Globulin	0.55	1.32	1.08	0.68
Beta Globulin	0.70	1.36	1.26	1.22
Gamma Globulin	1.35	2.86	1.75	1.98
Cryoglobulin	..	1.00	0.10	++

(Albumin and globulin fractionations represent average peak values.)

Comment. This 33-year-old Negro man is thought to have scleroderma with demonstrable involvement of the hands, heart and gastrointestinal tract. The role of cryoglobulinemia is unknown. As far as we can determine it has not been previously found in scleroderma. It is thought that the cryoglobulins may contribute to the cold sensitivity, digital gangrene, retinal artery

occlusion and possibly the patient's sudden brief psychotic episode[25].

CASE 2. W. W., a 66-year-old Negro man, was admitted to the Veterans Administration Hospital, Philadelphia, on December 29, 1954. The patient, a cook in the Merchant Marines, had been working in Hawaii since 1949 and had returned to this country 6 weeks prior to admission. One week later, following exposure to the cold weather, he noticed numbness in his right hand, accompanied by a sensation of severe cold. This was followed by purplish discoloration of the distal half of the right index and middle fingers. Due to the persistence of these complaints, hospitalization was advised.

The past and family histories were not remarkable.

On admission, the positive findings on physical examination were limited to the right upper extremity. The radial and brachial pulses were not palpable on the right and the tips of the middle and index fingers were cold and blue (Fig. 1). The blood pressure was 72/60 on the right, 118/60 on the left. Peripheral pulses were normal in the left arm and lower extremities. The remainder of the physical examination was within normal limits.

Fig. 1.—CASE 2. Photograph showing gangrenous changes of the tips of the middle and index fingers of the right hand.

Laboratory studies revealed normal hemogram, urinalyses and blood chemistries with the exception of the serum protein studies (Table 1). A persistent hyperglobulinemia was present, revealed by electrophoresis to be due to a generalized increase in the globulin fraction. On cooling the patient's serum to 4° C. a definite turbidity was noted within

72 hours. Heating resulted in prompt clearing of the serum. By centrifuging cooled serum and determining the protein content of the supernatant fluid, the amount of cryoglobulin was estimated to be 100 mg. per 100 cc. Roentgenograms of the long bones, skull, spine, pelvis and chest revealed no findings of significance. The results of sternal marrow aspiration were within normal limits. An electrocardiogram was normal. Cold agglutinins and serological tests for syphilis were negative. There was no Bence Jones proteinuria.

Fig. 2.—CASE 3. Photograph showing digital gangrene.

Oscillometric determinations confirmed the markedly decreased pulsations in the right upper extremity. Vasoconstriction by cold produced a fall in skin temperature and significant rises in skin temperature were produced by vasodilatation with heat and by stellate ganglion block. A right cervical sympathectomy was performed on January 25, 1955. The patient did well postoperatively. The right hand became warm and the gangrenous areas disappeared. When last seen in March, 1955, hyperglobulinemia, cryoglobulinemia and cold sensitivity remained.

Comment. Arteriosclerotic vascular occlusion seems very likely in this patient. The favorable response to cervical sympathectomy seems to indicate an element of vasoconstriction. The role of the cryoglobulins in the production of the arterial occlusion is unknown. It is possible that the precipitation of cold sensitive globulins in the presence of diminished vascular reserve was responsible for the development of gangrene. None of the usual underlying diseases associated with cryoglobulinemia has been demonstrated.

CASE 3. C. M., a 59-year-old white male, was admitted to the Veterans Administration Hospital, Philadelphia, on December 4, 1954.

The patient had known rheumatic heart disease with mitral stenosis for at least 15 years and had auricular fibrillation for at least 8 years. He had no cardiac symptoms on 100 mg. digitalis daily. For about 5 years the patient had noticed increasing sensitivity of the fingers to cold. Several weeks prior to admission gangrenous changes had developed on the tips of several fingers.

Physical examination revealed a well de-

veloped and nourished white male in no distress. Examination of the heart revealed a grossly irregular rhythm with a ventricular rate of 80. Apical systolic and diastolic murmurs were present. The fingers of both hands were cyanotic and cold and there were gangrenous changes of several finger tips (Fig. 2). The peripheral pulses, however, were of good quality. The remainder of the physical examination was within normal limits.

Laboratory studies revealed a normal hemogram and urinalyses. Cold agglutinins and serological test for syphilis were negative. Tests of renal and hepatic function yielded normal values. Blood chemistries were within normal limits except for the serum proteins; hyperglobulinemia was consistently present. Electrophoretic protein fractionation is shown in Table 1. An electrocardiogram revealed auricular fibrillation with a well controlled ventricular rate. Cardiac roentgenography revealed an enlarged left auricle. Roentgenograms of the skull, pelvis, spine and long bones were within normal limits. A sternal marrow aspiration was normal. There was no Bence Jones proteinuria. Cryoglobulinemia was present.

Vasoconstriction by cold revealed a fall in the skin temperature of the hands. A significant rise in temperature was produced by heat and stellate ganglion blocks. Bilateral cervical sympathectomy was performed in 2 stages. The postoperative course was excellent. The hands became warm and skin changes regressed except in the left 4th finger where gangrene became demarcated, necessitating amputation of the distal phalanx. During his hospitalization the patient developed increasing signs of vascular insufficiency in his lower extremities and bilateral lumbar sympathectomy was performed with excellent results.

The patient was discharged from the hospital on March 14, 1955.

Comment. Occlusive vascular disease due to arteriosclerosis is the probable diagnosis in this case. Embolic phenomena from a fibrillating auricle of long standing rheumatic heart disease seems less likely. Cryoglobulins have been described in rheumatic heart disease[8,21] and their precipitation may have been responsible for the occurrence of gangrene in the presence of the patient's diminished vascular reserve.

Discussion. A definite relationship between the occurrence of cryoglobulinemia and the presence of occlusive vascular disease in the 3 cases presented cannot be established. It seems reasonable to assume, however, that the precipitation of cold sensitive proteins may provoke gangrenous changes when the vascular reserve is impaired. In Case 1, the underlying vascular defect is probably due to scleroderma and in Cases 2 and 3, arteriosclerosis. The clinical picture of sensitivity to cold, involvement of the upper extremities, hyperglobulinemia and cryoglobulinemia is similar in all 3 cases.

Multiple myeloma has usually been present in the previously reported instances of cryoglobulinemia associated with cold sensitivity and Raynaud's phenomena. In the case of gangrene of the digits associated with cryoglobulinemia, reported by Hutchinson and Howell[17], multiple myeloma could not be demonstrated although bone marrow aspiration revealed 15% plasma cells, many with multiple nuclei. Cugudda[7] reported a patient with multiple myeloma and cryoglobulinemia who developed gangrene of a lower extremity, necessitating amputation. Neither multiple myeloma nor any other disorder commonly associated with hyperglobulinemia has been diagnosed in the patients presented. Scleroderma, the probable diagnosis in Case 1, is occasionally associated with disturbances in globulin[19], but as far as can be determined, cryoglobulinemia has not been reported. Cryoglobulins have been noted in rheumatic heart disease, present in Case 3, but have not been associated with symptoms.

The cause of the hyperglobulinemia and origin of the cryoglobulins in the cases presented remain unknown. Plasma cells have usually been considered the source of the abnormal globulins in multiple myeloma but this has not been proved. This theory is difficult to apply in cases, such as the

patients presented here, where plasma cell hyperplasia cannot be demonstrated.

No specific electrophoretic pattern was noted in the 3 cases described, an increase in all globulin fractions being present. Studies were not performed to determine the specific globulin fraction containing the cold precipitable element. Previous studies have revealed cryoglobulins to have a relatively high molecular weight of 190,000 to 200,000 and to be contained in the gamma fraction[2,5].

The similarity in the manifestations of cryoglobulins and cold agglutinins suggests a possible relationship. In the case of chronic lymphatic leukemia reported by Schwartz and Jager[30], a cold precipitable protein and cold agglutinins were present in significant amounts. Their studies indicated that the property of cold agglutination was resident in the cryoglobulin itself. This association is apparently unique. Cold agglutinins were absent in the 3 cases presented here. Luckey[24] compared the behavior of blood containing cryoglobulins with that of a patient having a high cold agglutinin titer. He found that in the case of cryoglobulinemia, pseudoagglutination with precipitation of protein and physical enmeshing of red blood cells occurred. On cooling the serum containing cold agglutinins, there was diffuse clumping of the red blood cells with no precipitate.

Summary. Three cases of cryoglobulinemia, associated with cold sensitivity and gangrene of the digits, have been presented. None of the diseases usually associated with significant amounts of cold precipitable proteins have been demonstrated. One patient probably has scleroderma, the others occlusive arteriosclerotic disease, complicated by the presence of rheumatic heart disease in one.

Electrophoretic patterns revealed an increase in all globulin fractions. Cold agglutinins were absent.

Though a relationship cannot be definitely established, it seems plausible that precipitation of cold sensitive proteins in the presence of a diminished vascular reserve may result in arterial insufficiency and gangrene.

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SUMMARIO IN INTERLINGUA

Cryoglobulinemia Associate con Gangrena del Digitos

Es presentate tres casos de cryoglobulinemia associate con sensibilitate a frigido e gangrena digital. Nulle del morbos ordinarimente associate con significative quantitates de cryoprecipitabile proteinas esseva demonstrabile. Un del patientes habeva probabilement scleroderma. Le alteres habeva occlusive morbo arteriosclerotic. Isto esseva complicate in un caso per le presentia de rheumatic morbo cardiac.

Le configurationes electrophoretic indicava un augmento de omne fractiones globulinic. Cryoagglutininas non esseva presente.

Il pare plausible, ben que iste conception non es definitivemente demonstrabile, que le precipitation de cryosensibile proteinas pote, in le presentia de reducite reservas vascular, resultar in insufficientia arterial e gangrena.

OBSERVATIONS ON EPITHELIAL CELLS EXFOLIATED FROM THE UPPER GASTROINTESTINAL TRACT OF PATIENTS WITH PERNICIOUS ANEMIA, SIMPLE ACHLORHYDRIA, AND CARCINOMA OF THE ESOPHAGUS AND STOMACH*

By Barbara W. Massey, A.B.
RESEARCH ASSOCIATE, DEPARTMENT OF MEDICINE

AND

Melvin I. Klayman, M.D.
PUBLIC HEALTH SERVICE RESEARCH FELLOW OF THE NATIONAL CANCER INSTITUTE

(From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago, Illinois)

Characteristic changes are seen in squamous cells exfoliating from the upper gastrointestinal tract of patients with pernicious anemia in relapse. Multinucleation, atypical chromatin pattern and increase in cell size (Fig. 1) are present in 30% or more of the exfoliated cells. Following adequate therapy the squamous cells return, for the most part, to normal (Fig. 2)[2]. Columnar cells from the gastric mucosa also show characteristic changes in pernicious anemia in relapse. The nuclei are twice normal size with creased or folded nuclear membranes and a finely stippled chromatin network (Fig. 8). Unlike the squamous cells, the large "bland" columnar cells persist after therapy and probably reflect the irreversible gastric atrophy found in all patients with pernicious anemia[3].

These findings suggested that this cytologic picture of atypical squamous and columnar cells might prove specific for pernicious anemia in relapse; and that the presence of the large gastric columnar cells alone might be diagnostic for pernicious anemia in remission.

The present study was undertaken to test this hypothesis and to determine the specificity of these findings in a large group of patients with other types of anemia, simple achlorhydria, esophageal and gastric malignancy.

Material and Methods. Cytologic material was collected from the stomach via a Levin tube by lavage with Ringer's solution and buffered chymotrypsin; then stained in the manner described previously[5]. The staining procedure was modified by the substitution of EA 36 for EA 65. It has been our experience that hematoxylin fades within a few months when EA 65 is used, whereas with EA 36 the stain is much less changed after a year. The antral abrasive balloon was not used.

Of 27 patients† with pernicious anemia, 10 were in hematologic remission and 17 were in relapse by the generally accepted hematologic criteria. Nine of the patients first studied during relapse were re-examined 1 to 17 months after institution of therapy. Sixty-three patients with simple achlorhydria after Histalog** stimulation and without specific evidence for pernicious anemia were tested. Fifty-seven cases of gastric cancer and 21

*This study was facilitated by grants from the Illinois Branch of the American Cancer Society and the Stewart Fund to the University of Chicago.

†Grateful acknowledgement is made to Dr. Steven O. Schwartz, Department of Hematology, Cook County Hospital, Chicago, for permitting us to study 9 patients with pernicious anemia.

**Kindly supplied by Eli Lilly & Co.

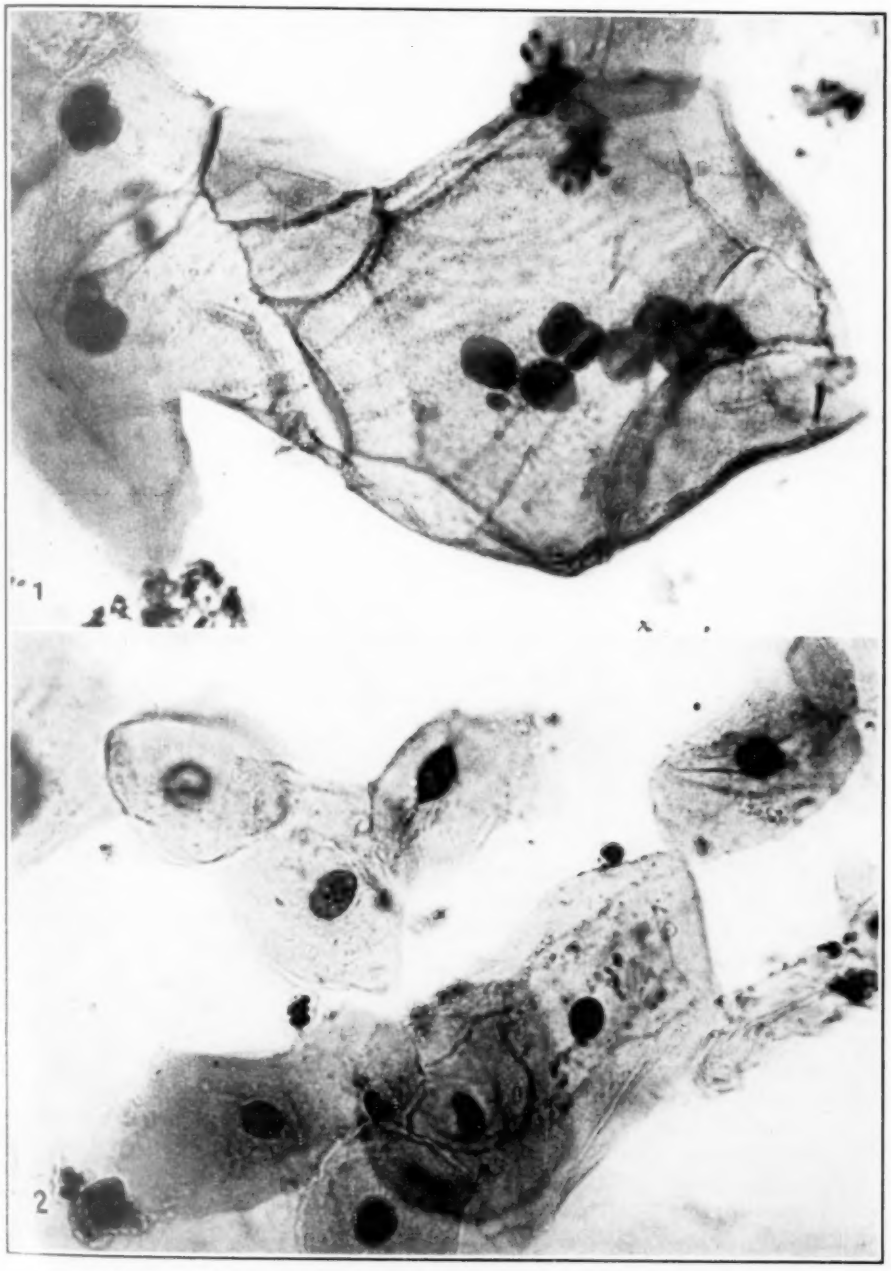

Fig. 1.—Large, multinucleated squamous cell; pernicious anemia in relapse. × 750

Fig. 2.—Normal superficial squamous cells; pernicious anemia in remission. × 750

of esophageal malignancy were also examined, as were 46 cases of nonpernicious anemia.

The vitamin $B_{12}CO_{60}$ test for intrinsic factor activity described by Schilling[7] was performed in 12 patients of the achlorhydria group.

Results. PERNICIOUS ANEMIA GROUP. In the gastric smears from 10 patients with pernicious anemia in remission (duration of disease, 2 to 16 years) a normal squamous cell pattern (Fig. 2) was found plus the large "bland" columnar cells associated with pernicious anemia (Fig. 8). The addition of this group to the 21 patients with pernicious anemia in remission previously reported[3], brings the series examined in this laboratory to 31, all of whom were found to have the same cellular picture.

Of the 17 patients with pernicious anemia in relapse, 14 had the atypical squamous cells (30% or more of the cells affected) described by Graham and Rheault. In these patients, there was no apparent correlation of the hemoglobin level to the presence of atypia. Six of the 14 patients with marked atypia had hemoglobin values of 10 gm. or more per 100 cc. of blood and 2 of the 3 patients with normal squamous cells had hemoglobin values below 8 gm. per 100 cc. Fourteen of the 17 patients with pernicious anemia in relapse exhibited the large "bland" gastric columnar cells. The absence of these cells in 3 patients is in keeping with our previous experience as they are not always recovered on the first test. It should be stressed that changes in the squamous cells are obvious at first glance because many of the cells are involved; in one patient 84% of the cells were abnormal. In contrast, large numbers of *normal* gastric columnar cells (Fig. 5) are usually seen and a careful search for the occasional large "bland" cells is necessary when the lavage method is used. This is true of the gastric cells before and after treatment.

In 9 patients first examined during relapse, a return to normal of the squamous cells but persistence of the large "bland" columnar cells was found after specific therapy.

The "active" columnar cells of pernicious anemia[3] merit further discussion. Because of the recognized increased incidence of gastric malignancy in patients with pernicious anemia, these cells are of great interest. The nuclei are twice normal size with prominent nucleoli and heavy irregular nuclear membranes. The cytoplasm is heavily granular and often contains small vacuoles (Fig. 6). In some instances, these cells are strongly suggestive of malignancy. The first time they were seen an erroneous diagnosis of carcinoma was made.

The recovery of "active" cells cannot be correlated with the duration of disease, state of therapy, or the presence of polyps. They were encountered in 7 of 28 patients with pernicious anemia. In 4 instances they were present in the initial smears prior to therapy but demonstrable in only one of 3 examined after therapy. Two patients had "active" cells one month and 6 months following institution of therapy but none were present on the initial smears. The final patient was examined cytologically for the first time after 16 years of therapy. The "active" cells in this case were considered as abnormal as columnar cells can appear and still remain nonmalignant (Fig. 6). Cells which are morphologically indistinguishable from the "active" cells of pernicious anemia (Fig. 7), were seen in 5 cases of gastric carcinoma not associated with pernicious anemia. These will be discussed below. They have also been observed by Rubin in one case of megaloblastic anemia of pregnancy[4].

It has been suggested that "active" cells may be correlated with the presence of gastric polyps[4]. Such a correlation is not present in this small series. Of 4 patients with polyps demonstrated by Roentgen ray or gastroscopy, "active" columnar cells were present in only one and of 7 with "active" columnar cells, only one had a demontrable polyp. However, more than one roentgenographic study or gastroscopy examination is often necessary either to establish or rule out the presence of polyps; and more than one cytologic examination may be needed to demonstrate "active" columnar cells.

NONPERNICIOUS ANEMIA GROUP. Sixty-three patients with achlorhydria after stimulation by Histalog but without pernicious anemia or gastrointestinal cancer were examined. In 14, large "bland" columnar cells, similar in all respects to those seen in pernicious anemia, were found. The pertinent clinical and laboratory findings are summarized in Table 1. The only constant finding was achlorhydria. It is interesting that 3 of these patients had a family history of pernicious anemia; intrinsic factor activity was tested for in 2 and shown to be normal. Pathologic material was available from one patient with a blood loss anemia, normal bone marrow and atrophic gastritis on gastroscopy. A subtotal resection was performed for gastric hemorrhage. Microscopic examination of the stomach disclosed marked gastric atrophy with complete loss of fundic glands and extensive intestinalization. The source of the large "bland" columnar cells could not be demonstrated as has been our previous experience with histologic material[3].

The "bland" columnar cells were seen once in a patient who had small amounts of hydrochloric acid. A subtotal gastric resection was performed for gastric ulcers. Histologic sections of the stomach revealed extensive atrophy and intestinalization with a rare patch of normal fundic mucosa remaining.

Forty-six patients with anemia of various etiologies were examined. Seventeen had achlorhydria; 6 of these had "bland" columnar cells (see Table 1). There is no apparent correlation between nonpernicious anemia and atypicality of the columnar cells.

Aberrations in the squamous cells (30% or more of the cells affected) similar to those seen in pernicious anemia have been observed in 4 patients who had neither pernicious anemia nor gastrointestinal malignancy. No organic disease was demonstrated in one patient, another had achlorhydria and anemia of unknown etiology. A third patient, examined 6 years after subtotal gastric resection, with achlorhydria and the "dumping" syndrome, also had these atypical squamous cells. The fourth patient had a megaloblastic anemia secondary to a massive small bowel resection for regional enteritis. The absorptive defect was confirmed by the absence of radioactivity in the urine following the vitamin $B_{12}Co_{60}$ test. The presence of hyperchlorhydria on gastric analysis excluded the possibility of pernicious anemia. The squamous cells returned to normal following vitamin B_{12} therapy.

CANCER GROUP. In a large series of gastric and esophageal carcinomas, atypia of the nonmalignant cells similar to that of pernicious anemia has been encountered in 6 instances. The squamous cell pattern of pernicious anemia in relapse was present in one patient with an esophageal carcinoma without anemia (Fig. 3). The cells were greatly enlarged and multinucleated, but the atypical nuclear chromatin pattern usually seen in pernicious anemia was not generally present.

Large "bland" or "active" columnar cells were found in 5 cases of gastric carcinoma; 2 of these had the atypical

TABLE 1.—NONPERNICIOUS ANEMIA PATIENTS WITH LARGE "BLAND" COLUMNAR CELLS

Name and Unit No.	*Achlorhydria*	*Anemia at Time of Cytology*	*History of Treated Anemia*	*Megaloblastic Bone Marrow*	*Normal Intrinsic Factor Activity by B_{12} Co^{60} Test*	*Gastroscopic Diagnosis of Atrophy*	*Family History of Pernicious Anemia*
1. E. B. 601299	+	—	+	0	0	0	—
2. M.B. 588877	+	+	—	—	0	+	—
3. F.B. 593161	+	—	+	—	+	+	—
4. A.C. 601077	+	—	+	0	+	0	+
5. W.G. 170521	+	+	—	—	+	+	—
6. A.G. 496810	+	—	—	—	+	+	—
7. B.G. 572978	+	+	—	0	0	0	+
8. O.H. 233613	+	—	—	—	+	+	—
9. L.J. 594887	+	+	+	—	+	0	+
10. M.P. 008498	+	—	—	0	+	0	—
11. S.P. 521990	+	+	—	0	0	0	—
12. G.P. 603775	+	+	—	—	+	0	—
13. J.R. 585349	+	—	—	0	+	+	—
14. P.V. 517515	+	—	—	0	+	0	—

Key: + = Present
— = Absent
0 = Not examined

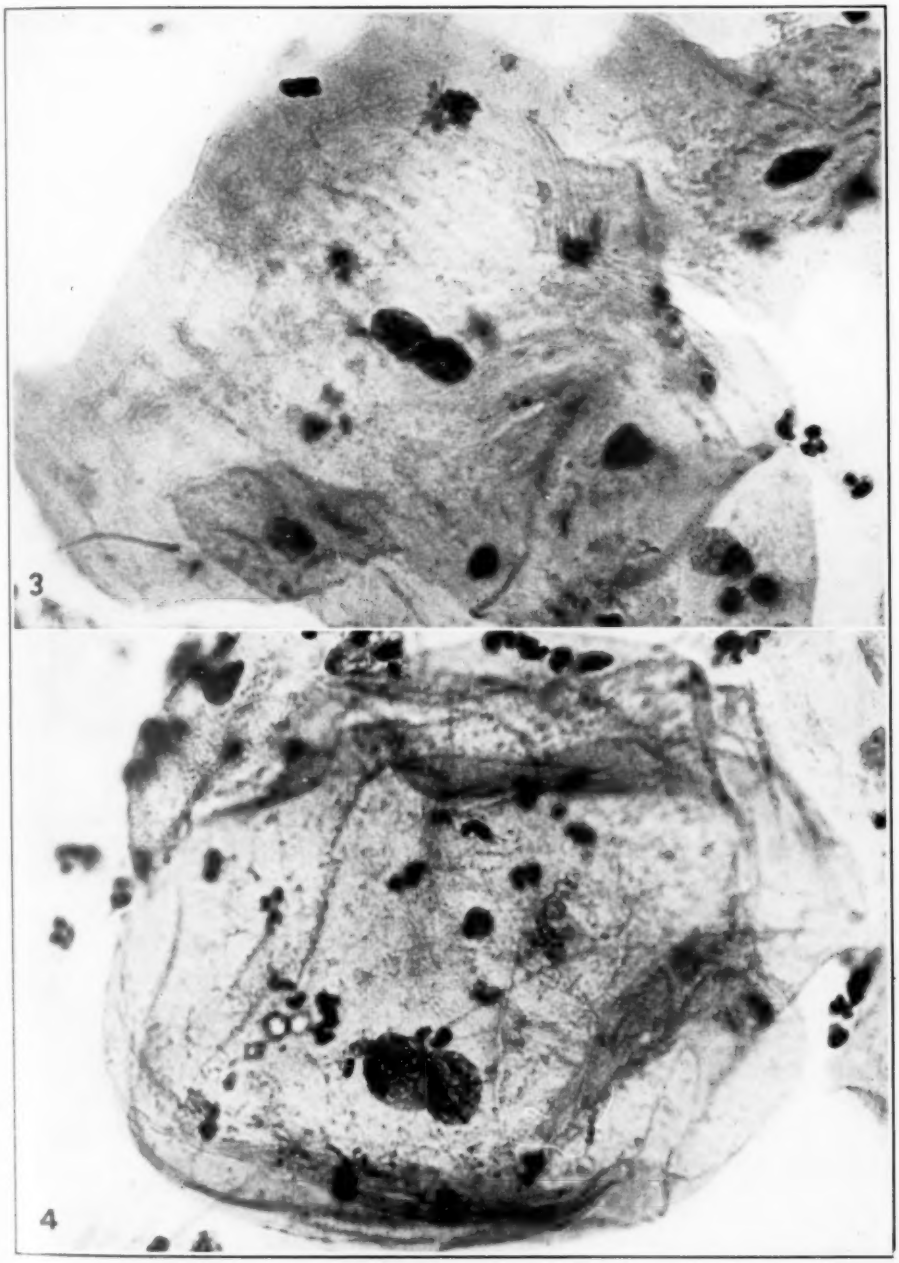

Fig. 3.—Large, double-nucleated squamous cell; esophageal carcinoma. × 750

Fig. 4.—Large, double-nucleated squamous cell; after radiation therapy. × 750

squamous cells also. The "bland" columnar cells were seen once in a patient who had achlorhydria and blood loss anemia due to an inoperable gastric neoplasm. The squamous cells in this patient were normal. Two other patients with achlorhydria had "active" columnar cells with normal squamous cells. One had a history of an unidentified anemia treated with liver injections and iron. The other patient had severe anemia on admission considered secondary to his gastric carcinoma. The cytologic picture of atypical squamous cells and large "active" columnar cells was seen in 2 patients with gastric carcinoma. Both secreted small amounts of acid; neither had anemia.

It should be noted that the diagnosis of cancer was made in these 5 cases on cells of unequivocal malignancy (Fig. 9). The "active" columnar cells (Fig. 7) must, in our present state of knowledge, be considered nonmalignant.

Discussion. The striking squamous cell changes seen in pernicious anemia in relapse, while characteristic, are not specific for the disease since they may be found in other anemias and in carcinoma. Because they are reversible after vitamin B_{12} therapy, these atypical squamous cells may reflect a generalized nutritional deficiency. It is of interest to note that radiation reaction causes squamous cell changes essentially the same as those seen in untreated pernicious anemia. The phenomena of cell enlargement, cytoplasmic vacuolization, multinucleation and atypical chromatin pattern were first described by Graham in nonmalignant squamous cells from the vagina and cervix after Roentgen-ray and radium therapy for carcinoma of the cervix[1]. In this laboratory, the same changes have been noted in the squamous cells from the esophagus following radiation treatment for peptic ulcer (Fig. 4). The cytoplasmic vacuolization present after radiation is the only alteration not seen in the atypical squamous cells of pernicious anemia and carcinoma. These observations suggest that the squamous cells have a limited reaction pattern; the cellular response appears to be the same although the causes are different.

The large "bland" columnar cells seen in pernicious anemia reflect a permanent change in the gastric mucosa. These cells may also be seen in patients with achlorhydria or severe gastric atrophy and are therefore not specific for pernicious anemia. Whenever pathologic material has been available from patients (with or without pernicious anemia) who have demonstrated these large "bland" cells, severe and extensive gastric atrophy has been found.

"Active" columnar cells difficult to distinguish from malignancy are seen in some cases of pernicious anemia. They have not been found thus far in our experience in achlorhydria or nonpernicious anemia patients except when gastric carcinoma was present. The prognostic significance of these cells cannot be stated at this time. However, the cytologically malignant-appearing mucous cells observed by Schell *et al.*[6] surrounding the gastric tumor and microscopic areas of carcinoma in patients with pernicious anemia may be related to these exfoliated malignant-appearing cells. Careful observation of patients with "active" columnar cells is necessary in order to establish the possible relationship of these cells to carcinoma.

Summary and Conclusions. 1. Pernicious anemia in relapse presents an unusual cytologic picture of enlarged, atypical squamous and columnar cells characteristic of the disease, but not specific for it. Following adequate

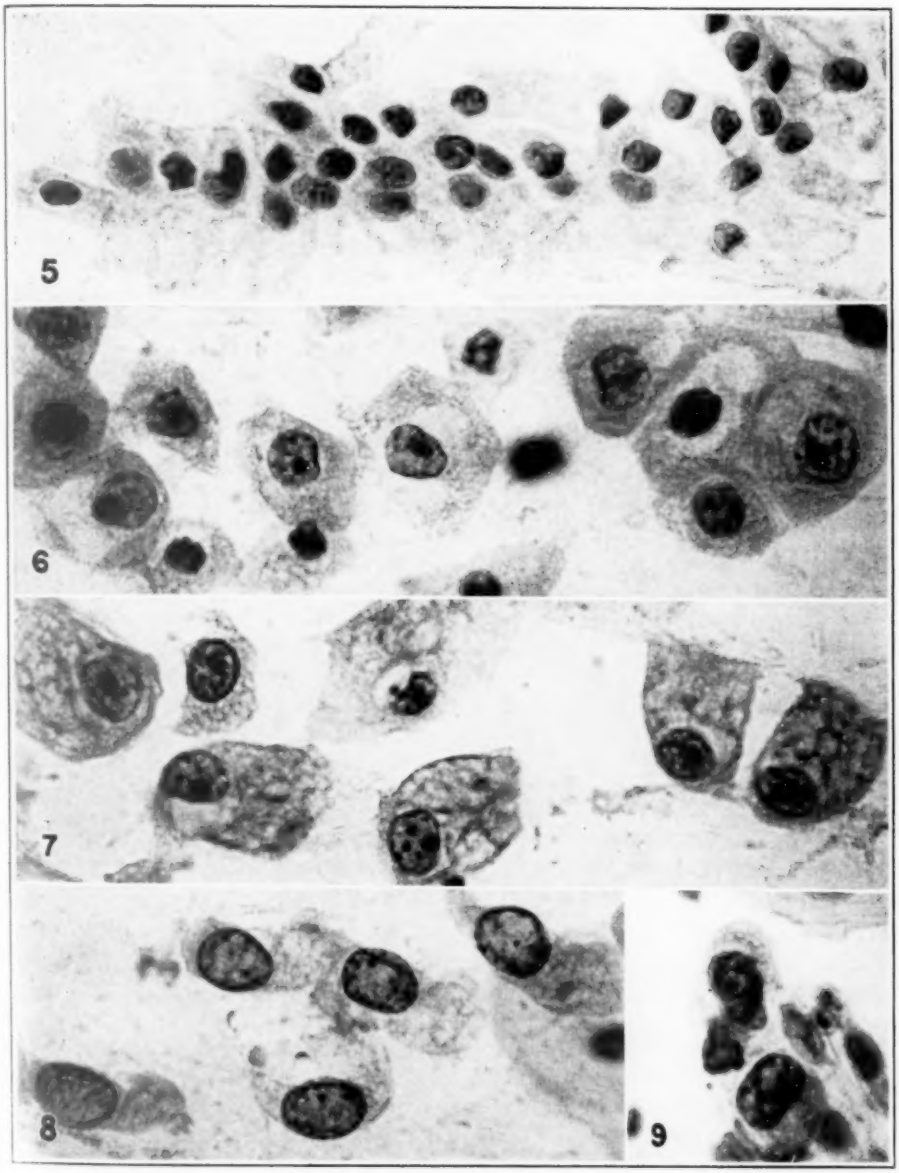

Fig. 5.—Normal columnar cells; pernicious anemia in remission. × 750

Fig. 6.—"Active" columnar cells; pernicious anemia in remission. × 750

Fig. 7.—"Active" columnar cells; gastric carcinoma. × 750

Fig. 8.—Large "bland" columnar cells; pernicious anemia in remission. × 750

Fig. 9.—Malignant cells; gastric carcinoma (same case as Fig. 7). × 750

therapy the squamous cells return to normal, but the large columnar cells persist.

2. Changes in the squamous cells similar to those of pernicious anemia may be seen in other nutritional deficiencies, in carcinoma of the esophagus and stomach, and after radiation therapy.

3. The large, "bland" columnar cells characteristic of pernicious anemia may be found in some patients with simple achlorhydria, gastric atrophy or carcinoma of the stomach.

4. The "active" columnar cells seen in some patients with pernicious anemia are also found in some cases of carcinoma of the stomach.

5. The significance of these findings is discussed.

ACKNOWLEDGMENTS: We are grateful to Miss Sylvia Pleticka for cytologic assistance; to Drs. Walter L. Palmer and Joseph B. Kirsner for their interest and encouragement; to Mr. Jean Crunelle for the photographs. We are indebted to the Armour Laboratories, Kankakee, Illinois, for generous amounts of chymotrypsin, and to Merck & Co., Rahway, New Jersey, for the vitamin $B_{12}Co^{58}$ and vitamin B_{12}.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Observationes Super Cellulas Epithelial Exfoliate ab le Tubo Gastro-Intestinal Superior de Patientes con Anemia Perniciose, Achlorhydria Simple, e Carcinoma de Esophago e Stomacho

1. Anemia perniciose in casos de relapso presenta un inusual configuration cytologic de atypic e allargate cellulas squamose e columnar que es un tracto characteristic sed non specific del morbo. Post un therapia adequate le cellulas squamose retorna al norma sed le cellulas columnar persiste.

2. Cellulas squamose con cambiamentos simile a illos incontrate in anemia perniciose es a vices etiam observabile in altere deficientias nutritional, in carcinoma del esophago e del stomacho, e post therapia a irradiation.

3. Le grande e "suave" cellulas columnar que es un characteristica de anemia perniciose se trova etiam in certe patientes con achlorhydria simple, atrophia gastric, o carcinoma del stomacho.

4. Le "active" cellulas columnar que es observate in alicun patientes con anemia perniciose se incontra etiam in certe casos de carcinoma del stomacho.

5. Le signification de iste constatationes es discutite.

VARICES OF THE DISTAL ESOPHAGUS IN THE APPARENT ABSENCE OF PORTAL AND OF SUPERIOR CAVAL HYPERTENSION

By Eddy D. Palmer, Lt. Col., MC
CHIEF, GASTROENTEROLOGY SERVICE

AND

Irving B. Brick, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Gastroenterology Services, Walter Reed Army Hospital, and Georgetown University Hospital and School of Medicine, Washington, D. C.)

Increasing enthusiasm among internists over the value of esophagoscopy with telescopic magnification for the study of esophageal varices has recently brought to light several new problems which must be faced before the handling of patients with varices can be considered satisfactory. Of fundamental importance, of course, has been the revelation, perhaps a rather unexpected one, that there has been serious ignorance of the natural history of esophageal varices and of portal hypertension. Even the simple mechanisms responsible for elevation of portal pressure and the diseases which may be accompanied by varices have by no means been satisfactorily identified. The cirrhoses, schistosomiases, and the many causes of portal vein block are usually thought of as the main causes of varices, and it has long been known that varices may, on occasion, accompany secondary amyloidosis, polycythemia vera, kala azar, fascioliasis, chlonorchiasis, hepatoma, liver abscess, polycystic liver, Chiari's disease, metastatic carcinoma of the liver, chronic cholangitis, sarcoidosis, and the superior vena caval hypertension syndromes, such as those due to Pick's disease, superior mediastinal tumors, chronic congestive heart failure, and intrathoracic arteriovenous aneurysms. In local experience we have been impressed with the observations that varices of serious size and extent, presumably capable of serious hemorrhage, may also occur in normal pregnancy, amebic hepatitis, acute viral hepatitis, simple portal fibrosis, fatty liver, and achalasia[8,9]. All of these represent the usual type of distal or mid-esophageal varices, secondary to venous hypertension.

There are three other general classes of esophageal varices. First, there is a rare form of apparently true primary varices, limited to the uppermost portion of the esophagus, and believed due to venous congestion produced by the cricopharyngeus muscle on abnormal caudad extensions of the posterior hypopharyngeal plexus[7]. Second, there are cases of varices with portal hypertension but without any clinical or anatomic explanation for the portal hypertension[3].

The third type, the subject of the present communication, is the instance of idiopathic varices of the distal esophagus which seem to exist in the absence of either portal or superior caval hypertension. This is a difficult diagnosis to make, unless the venous pressure within the varices is measured directly. The absence of other clinical signs of venous hypertension is not necessarily proof of normal portal or caval pressure. Furthermore, the anatomy of a

diseased portal venous system is such that it is possible for various of its portions to be under different heads of pressure. A few apparently valid cases have been reported, at least two in children[1,2,4-6]. Most of these patients came to medical attention because of hemorrhage. It is possible that true primary varices of the distal esophagus are not rare, but, unless there be hemorrhage, they do not make their presence known. By definition, this form of varices is unattended by any other abnormality.

The purpose of this presentation is to record our observations on such cases, including their incidence, significance, etiology, recognition and management.

TABLE 1.—350 CASES OF ESOPHAGOSCOPICALLY DIAGNOSED ESOPHAGEAL VARICES: ETIOLOGIC DISTRIBUTION

237	portal cirrhosis (including hemochromatosis)
17	schistosomiasis
1	amebic hepatitis
15	portal fibrosis
6	fatty liver
3	hepatoma
1	polycystic liver
2	hemosiderosis of liver
5	metastatic liver disease
14	acute viral hepatitis
8	chronic heart failure
6	normal pregnancy
15	portal vein block
1	Chiari's disease
3	achalasia
3	primary varices of cervical esophagus
13	of distal esophagus without venous hypertension

Material. During the past 5 years we have studied and treated 350 patients with esophagoscopically diagnosed esophageal varices. Their etiologic distribution is shown in Table 1. Among these there were 13 patients who appeared to have neither portal nor superior caval hypertension. The portal pressure was actually measured in only 4 cases, three transesophagoscopically within the variceal lumen, and one at laparotomy in the portal vein, and it was 190 mm. of water or less in each. In none of the patients was there splenomegaly, hepatomegaly, ascites, distended abdominal veins, or any signs of supradiaphragmatic venous engorgement. Except for epigastric tenderness in one patient with active duodenal ulcer, abdominal examination was normal in all patients. Liver biopsy and full battery of liver function tests were normal in all and repeatedly so in some. It was believed that liver disease had been excluded with assurance and that portal and caval hypertension had been excluded by all practical means. It is unfortunate that the portal pressure was not obtainable in all patients, but one of the hospitals taking part in the study is not equipped for the transesophagoscopic technique and, in addition, it has been found that it is particularly difficult to obtain clearly valid measurements under the conditions of slight or absent portal hypertension.

OBSERVATIONS. There were 9 men in the group. One patient was a Negro, the others, Caucasians. At the time of study 2 patients were in the third decade of life, 3 in the fourth, 3 in the fifth, 2 in the sixth, 2 in the seventh, and one in the eighth.

Nine of the 13 patients came to medical attention because of bleeding by mouth. Eight of the 9 were found also to have esophagitis. The bleeding had two characteristics. First, no episode had been particularly severe but had in most patients been repeated several times in the past. Eight of the 9 patients had been studied elsewhere at the time of a previous hemorrhage, but no diagnosis had been made in seven. A duodenal ulcer had been found in one. None had previously been examined esophagoscopically. Second, 4 of the 9 bleeders stated that, although they had had true vomiting during bleeding episodes, they believed that the blood had first welled up in the throat and was then swallowed before being vomited.

The 4 patients without a history of bleeding were examined because of either dysphagia or epigastric pain. In addition to varices, hiatus hernia was found in two and esophageal diverticulum in one.

Other diagnoses among the 13 pa-

tients included asthma (1 patient), duodenal ulcer (2 patients), hiatus hernia (3 patients), subacute erosive esophagitis (8 patients), simple gastroenterostomy of 25 years' standing (1 patient), emphysema (2 patients), and treated carcinoma of prostrate without demonstrable metastases (1 patient).

The extent and severity of the varices, as measured esophagoscopically, are outlined in Table 2. In most cases the mean diameter of the varices was classed as mild (3 mm. or less), but the length of the esophagus involved was moderately extensive. In all cases the varices were largest at the esophagogastric junction and became smaller in their cephalad extensions. There was change in diameter or extent in 5 of the 8 patients who were examined esophagoscopically more than once. These changes are found in all types of varices, and, even though they occurred over rather brief periods, they were recognized without surprise.

TABLE 2.—EVALUATION OF THE VARICES: SEVERITY AND EXTENT OF ESOPHAGUS INVOLVED UPON SUCCESSIVE EXAMINATIONS

Case	*Hemorrhage*	*First examination*	*Interval, weeks*	*Second examination*	*Interval, weeks*	*Third examination*
1	X	mild, 1/2				
2	O	mild, 1/2				
3	X	mod., 2/3	2	mod., 2/3	4	mild, 2/3
4	X	mod., 2/3				
5	X	mild, 1/3	3	mod., 1/2		
6	X	mild, 1/3	4	mild, 1/3	11	mild, 1/3
7	X	mod., 1/3	3	mod., 1/2		
8	X	mod., 1/3	6	mild, 1/3		
9	X	mild, 1/6	18	mild, 1/3		
10	X	mild, 1/3				
11	O	mild, 1/4	3	mild, 1/4		
12	O	mild, 1/3	3	mild, 1/3		
13	O	mild, 1/3	3	mild, 1/3		

TREATMENT. Four of the bleeders were hospitalized during active bleeding and were examined esophagoscopically following ice-water lavage. The bleeding was seen to be issuing from the varices. Tamponade treatment with the Sengstaken tube quickly stopped the bleeding in each, and there was no recurrence during the period of observation.

Definitive treatment was conservative in all but one case. This patient, who was studied because of a history of recurring hemorrhage, was found to have a duodenal ulcer, esophagitis, and moderate-sized varices of two-thirds of the esophagus. It was not possible to obtain a valid transesophagoscopic measurement of the portal pressure. A splenoportagram showed the varices and a patent portal vein. The patient was opened for portacaval shunt, but the portal pressure was found to be only 180 mm. of water. The surgeon believed that under these circumstances the varices had probably not been responsible for the bleeding episodes, and, therefore, performed a subtotal gastrectomy for the ulcer.

Conservative treatment in the other patients took the form of bismuth subcarbonate therapy for the seven with esophagitis and little but explanation for the rest.

COMMENT. One of the problems which has arisen as a consequence of use of telescopic equipment with the esophagoscope is the matter of just what constitutes a varix. A 4-diameter telescope gives an unbelievably better

view of the organ than does the esophagoscope by itself. Fine details can be studied clearly. Paradoxically, better visibility sometimes creates a problem in proper interpretation. Small veins are now seen in esophagi which would be called normal if magnification were not used. We believe that an abnormality is implied any time that veins which elevate the esophageal mucosa can be demonstrated under 4-diameter magnification when the patient is at rest. Sometimes small vessels can be seen in the mucosa of an apparently normal esophagus. When these actually elevate the mucosa, a matter easily determined from the surface highlights, we suspect they indicate abnormality. The exception is found in an occasional patient whose mucosa is smooth until he carries out a Valsalva effort, whereupon small straight veins arise. We do not believe this to be a sign of an abnormal state.

Using these criteria for arbitrarily defining a dividing line between normal superficially-placed esophageal veins and varices, we have to date observed only these 13 cases of varices in the distal esophagus which we could not explain on the basis of venous hypertension. Actually, in each of the 13 patients the varices were large enough so that proper interpretation did not create a problem, and additional confidence came from the finding of continued abnormality upon repeat examination. But questions have arisen for us over this problem in cases of cirrhosis, and in such cases it has been clear that some concrete definition, such as that stated above, must eventually be agreed upon, if there is to be proper intercourse over the matter of surgical portal decompression.

It appears rather singular that eight of the patients reported here were found to have esophagitis. After rather extensive experience with the microscopic study of mucosa removed by biopsy in cases of esophagitis, we believe that macroscopic venous engorgement is not part of the pathologic process of esophagitis. Rather, the explanation appears to lie in the assumption that esophagitis superimposed on esophageal varices is the factor responsible for the initiation of hemorrhage, and in the fact that in all patients with esophagitis it was hemorrhage which drew attention to the presence of varices.

Summary and Conclusions. It appears that varices of the distal esophagus may develop and exist in the absence of portal and superior caval hypertension, under a head of venous pressure which is not greater than that which normally exists in the portal system. Thirteen cases are discussed, these representing 3.7% of the patients with esophageal varices which have been studied esophagoscopically. The diagnosis is difficult to establish because, unless the venous pressure can be measured directly within the varices, it is a diagnosis of exclusion.

Esophageal varices in the absence of venous hypertension may be responsible for hemorrhage, although in the present experience bleeding has not been particularly severe. It is probable that esophagitis is responsible for initiation of the hemorrhage.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Varices del Esophago Distal con Apparente Absentia de Hypertension del Venas Portal e Cave Superior

Il pare que varices del esophago distal pote occurrer, in le absentia de hypertension portal e supero-cave, sub un pression venose que non excede le norma del systema portal. Nos discute 13 casos pertinente, representante 3,7 pro cento del patientes con varices esophagee que nos has studiate esophagoscopicamente. Le diagnose es difficile proque illo debe esser establite per un processo de exclusion si il non es possibile mesurar le pression directemente intra le varices.

Varices esophagee in le absentia de hypertension venose pote esser le causa de hemorrhagia. In nostre experientia, il es ver, le sanguination ha nunquam essite specialmente sever. Il es probabile que esophagitis es responsabile pro le initiation del hemorrhagia.

SUMMARIO IN INTERLINGUA

(See page 484 for original article)

Sanitate Public Fertilitate, e Economia General in lor Effectos Combinate Super le Standard del Vita

II. Evalutation Qualitative de Factores Responsabile pro le Conditiones Existente in Paises con Situationes Comparabile

Super le base del datos presentate in le prime articulo de iste serie, nos ha establite subdivisiones a confinios arbitrari—numerate ab 1 a 5—pro gruppar insimul ille paises e territorios que es characterisate per comparabile conditiones del fertilitate total, del pression del population, e del disveloppamento economic. Iste methodo monstra in cata caso individual si le conditiones es favorabile o disfavorabile per reguardo al nivello del existentia.

Le analyse del gruppos si obtenite—con consideration del elementos contribuente de natalitate, mortalitate, augmento e pression del population, e productivitate—permitteva signalar le effectos tanto favorabile como etiam disfavorabile de partial programmas de sanitate public. Illo etiam permitteva identificar le paises que pare incontrar le plus grande impedimentos a un melioration futur del nivello de existentia. Le resultatos—in iste articulo de natura predominantemente qualitative—demonstra le necessitate del uso de multiple componentes si nos visa a obtener un comprension general del conditiones real.

NEUROLOGICAL COMPLICATIONS FOLLOWING THE ADMINISTRATION OF SERA

By John B. MacGibbon, M.B.*
FELLOW IN MEDICINE, JOHNS HOPKINS HOSPITAL, BALTIMORE, MARYLAND

Since 1897, when Engelmann[4] reported the first case of a neurological complication of serum sickness, there have been, scattered throughout the literature, other reports of cases of this type. The early reports of Gardere and Gangolphe[5], Grumeberger[7] and Thaon[13] mentioned the occurrence of paralysis with serum administration but it was only the latter who suggested the association of the two. In France, especially, cases continued to appear and later reports came from England and this country. In 1931, Allen[1] had collected 42 cases from the literature. In 1932, Young[14] reviewed 50 cases, most of them from Europe, and presented a case of paralysis of the left arm following the administration of tetanus antitoxin. In the next year, Doyle[3] presented 2 cases of his own and reviewed 49. In 1954, from England, Miller and Stanton[8] presented 5 new cases and discussed the problem of neurological complications following sera, vaccinations and inoculations.

It would appear, considering the number of injections of serum that are administered, that this type of reaction is quite uncommon and it is likely that with the lessening use of sera in the treatment of such diseases as pneumonia, meningitis and scarlet fever that these reactions may become even fewer. However, one might well wonder whether these complications might not be more common than indicated by reports. The symptoms and signs may not be striking and may be hidden by more flagrant complaints of headache, malaise, fever, arthralgia, urticaria and edema. The nervous manifestations may come on late and go unrecognized as complications of serum sickness or they may be so transient that they are missed or not looked for. It was with this idea in mind that the Johns Hopkins Hospital records of 360 inpatients, who had a diagnosis of serum sickness, were reviewed. Two of the most interesting cases who had associated neurological complaints are presented in some detail, and 4 other similar cases are mentioned briefly in discussing the diagnosis and treatment of the complications.

Case Reports. Case 1. The first patient was a 29-year-old, white, male, steel worker (J.H.H. #200824) who was admitted to the Osler Medical Service on May 17, 1940, complaining of pains in his legs of 6 weeks' duration.

Nine weeks prior to his admission he had had the sudden onset of a severe sore throat and was told by his doctor that it was a streptococcal sore throat and about a week later he was given an injection of serum (probably streptococcal antiserum) into his buttocks. Six weeks before admission he was awakened with itching lumps on his lips, face and generally scattered over his body. For this he was given an injection by his doctor with immediate relief but a few days later he began to have severe pains on movement of his left knee. This persisted all the following week when he developed a similar pain in his left ankle. In spite of these symptoms he continued to work, but 3 weeks prior to admission he developed pains in the right knee and ankle. Pain in the right leg was intermittent but the pain in the left leg was persistent and he was forced to stop work 10

*Present address: Resident in Medicine, Church Home and Hospital, Baltimore 31, Md.

days before hospitalization. He complained, too, that for 2 weeks he had been having intermittent pains in the elbows and shoulders. Swelling had appeared only in the left ankle. He had not been conscious of fever. In addition, he complained that he had had intermittent episodes of involuntary twitching of his left leg and occasional severe cramps behind his left knee. The quivering was relieved when he got on his feet and walked and the cramps behind his left knee were relieved by straightening his leg out.

Physical examination revealed a healthy-looking, young, white male with a temperature of 99.5° F., and normal pulse rate, respiration rate and blood pressure. Positive findings included slight lateral nystagmus, dullness and thickening of both ear drums, pain on movement of the left shoulder, knee and ankle. There was some swelling and tenderness of both knees. On examination of the nervous system there was discovered a left Babinski response and ankle clonus. The knee jerk was brisker on the left and the left heel-knee test showed definite ataxia. The only abdominal reflex present was in the right upper quadrant.

During the patient's stay in the hospital, there was development of a transient macular rash over the face and neck, and the development of 10 to 15 purpuric spots over the dorsum of both feet. The neurological signs showed some variation and about 2 weeks after the first examination there was bilateral ataxia on both heel-knee tests, bilateral ankle clonus, unsteady station and ataxic gait. A biopsy of the gastrocnemius showed slight perivascular round-cell infiltration but no evidence of periarteritis nodosa.

In another 2 weeks' time the neurological signs had progressively disappeared but there was still a somewhat ataxic gait and there was some ataxia of the left finger-nose test.

Various diagnoses were entertained: rheumatic fever, multiple sclerosis, periarteritis nodosa and lupus erythematosus. It was thought that he might have some pallor of his temporal discs but this was not confirmed by the ophthalmological consultant. He was discharged from the hospital barely able to walk but in the weeks that followed he improved and after a few weeks he did not return again to the clinic.

He was seen, in his home in April, 1954, and stated that his symptoms had slowly cleared over a period of months. He said that he still had occasional twitching of the legs at night in bed but that otherwise he was well. His heel-knee test and his plantar responses were normal. His finger-nose test was normal and there was no nystagmus. His gait appeared normal. He was urged to come to the hospital for a complete neurological examination but failed to appear.

While he had been in hospital laboratory investigations, including roentgenograms of the chest, blood agglutinations, electrocardiogram and roentgenographic films of his joints failed to establish or lend weight to any specific diagnosis. His cerebrospinal fluid showed initial pressure of 82 mm. and there were no cells, protein was 25 mg. per 100 cc., the Wassermann was negative.

On reviewing the history, taking into account that the patient now appears well, and in the absence of any definite diagnosis of rheumatic fever it would seem reasonable to explain this man's symptoms on a single diagnosis of serum disease with neurological complications. Indeed, this was the diagnosis suggested by Dr. Warfield Longcope during the patient's hospitalization.

CASE 2. The second patient (E.H.) was a 32-year-old white female (J.H.H. #401185). Her previous health had been good except for a duodenal ulcer in 1951, an episode of diarrhea 2 months prior to her present visit, and some slight aching of the wrists, fingers and joints during damp weather for the past 10 years. She had a tonsillectomy in 1926.

Her present illness began 5 days prior to her first visit to the hospital when she was exposed to a presumed case of diphtheria. One day before the visit, she developed an acute sore throat accompanied by fever and general aching. When seen on October 7, 1953, she had an acutely sore throat and she was unable to swallow solids with any comfort. Her temperature was 98.8° F., her pulse rate 88 per min. and her respiration 19 per min. She had slight conjunctival injection. Her pharynx and soft palate were markedly injected. No definite exudate was seen but there was purulent postnasal discharge. There was no striking cervical adenopathy. The impression was that she had an acute pharyngitis, but with the history of a presumed diphtheria contact and a doubtful history of diphtheria immunization, it was decided to give her 40,000 units of diphtheria antitoxin at once and 600,000 units of penicillin daily. The antitoxin was administered after a negative routine skin test. A culture and a smear were taken at this time and the patient was sent home to bed. Later her smear was reported

as negative for diphtheria. On October 9, the patient returned to the clinic still with some soreness of her throat and some redness of the pharynx. On the evening of October 11, 1953, the patient visited the accident room because she had developed feverishness and tightness of the chest. She was found to have a temperature of 101° F. and a pulse rate of 100. As there were no other positive findings she was sent home with the tentative diagnosis of "grippe." Next day however, she returned with a burning, erythematous rash on her buttocks, spreading from the site of serum injection. In addition to these skin lesions, there was fever and slight generalized lymphadenopathy. She was assumed to be having a reaction to the antitoxin and she was given Pyribenzamine, 50 mg. every 4 hours. The next day she was much worse and the macular rash had spread over the entire abdominal wall. Her lymphadenopathy had increased and she complained of some stiffness in her joints, although there were no objective signs of this. Ephedrine and sedation were added to her therapy but with no improvement, for on the next day, October 15, 1953, she returned to the clinic with worsening of her complaints and also with conjunctivitis, chills, fever and very painful lymphadenopathy. The macular rash had disappeared but this had been replaced by a collection of urticarial wheals on both arms. Her temperature was 100° F. and her pulse rate 110.

She was admitted to the Osler Medical Service and she was described as well-nourished, well-developed, acutely ill, with a temperature of 102° F. and complaining of myalgia, arthralgia, sore throat, swollen, tender glands, and headache. On physical examination the positive findings were those of conjunctivitis and acutely tender, marked, generalized glandular enlargement. There was an erythematous blush to the skin with urticarial wheals over the extremities. The chest was clear, the heart sounds were normal and the abdominal examination within normal limits. Both wrists and metacarpophalangeal joints were swollen. There was diffuse injection of the conjunctivae and the pharynx.

Treatment was commenced with cortisone, Adrenalin in oil, Pyribenzamine and intravenous glucose.

In spite of heavy doses of cortisone, (650 mg. in 24 hours) she continued to have urticaria and angioneurotic edema throughout the day of October 16. By October 18, her symptoms had markedly improved, the angioneurotic edema had disappeared completely and the arthralgia and myalgia had also subsided. She was euphoric. Treatment with cortisone was continued at a level of 50 mg. every 6 hours. Her throat culture came back negative for diphtheria organisms. As she continued to improve, her cortisone was rapidly tapered without recurrence of symptoms and she was discharged on October 23.

Laboratory examinations immediately prior to admission to the hospital showed a shift to the left in her white count, with a 12% monocytosis and a total leukocyte count of 6,800 cells ber c.mm. The throat culture grew *Staphylococcus aureus* and alpha-streptococci. After admission to the hospital she developed a leukocytosis, varying from 11,000 to 14,000, a high percentage of juvenile polymorphonuclear cells and an elevated sedimentation rate. The heterophile agglutination titer was 1 in 2,560, unabsorbed, and with the guinea-pig kidney absorption test, was 1 in 40. Urinalysis on admission showed a trace of albumin. The levels of nonprotein nitrogen, carbon dioxide-combining power, chloride, bilirubin and proteins in the serum were within normal limits. The blood sugar level was also normal. Two blood cultures were sterile.

On October 27, two days after stopping cortisone, she had a slight return of her symptoms of serum sickness. She was complaining of pain in her shoulder girdle muscles and she said that this pain had been present ever since her admission to the hospital. Five days after stopping cortisone she was again seen complaining of pain in her shoulders, more so on the right, and she noticed a weakness in her right shoulder and a drawing sensation in the right upper arm. Her right shoulder felt clumsy and she was unable to abduct it. On examination she showed definite and striking winging of the right scapula, associated with weakness of the muscles of the right shoulder girdle, the sternomastoid, the trapezius, the spinati, the deltoid the biceps and especially the serratus magnus. No sensory loss was detected. The biceps and supinator reflexes on the right side were diminished. The impression was that she was suffering from a right brachial plexus neuritis and radiculitis affecting especially the long thoracic nerve of Bell.

At this same time she complained that she had some blurring of distant vision and the appearance of spots in front of both eyes, more especially the right eye. She stated that these symptoms had been present about 2 weeks but they had gone through several remissions and advancements and were now

severe enough to cause her to bring them to her physician's attention. She was examined by ophthalmologists and her eyes showed a slight circumcorneal congestion. The pupils were round, regular and reacted sluggishly to light and on accommodation with convergence. The intraocular tension was normal. Slit-lamp examination revealed a number of very small keratotic deposits, typical of the lymphoid cell type. There was a little fibrin in the anterior chamber and there was some edema of the iris. The fundi were negative. The vision was reduced to 20/40 in both eyes. The impression was that this was a typical picture of a nongranulomatous uveitis which in this case was complicating the general serum sickness. Local treatment with hydrocortisone and neomycin brought about a gradual improvement and disappearance of the ocular symptoms over the next month.

Her shoulder girdle lesion did not progress so favorably, and although she received physiotherapy and wore a Cavalier-type splint, 6 months later she still had considerable winging as can be seen in the illustration.

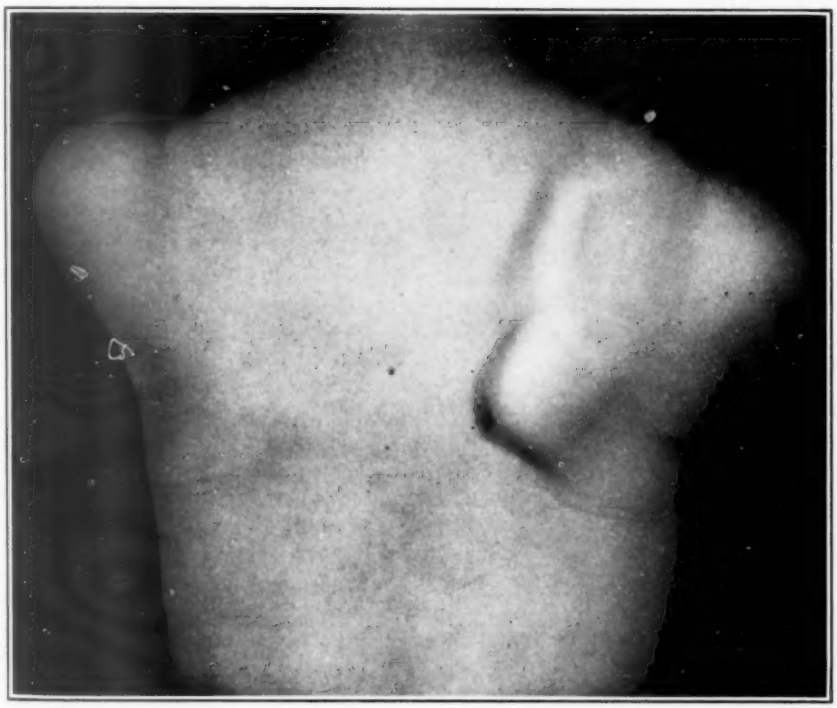

Fig. 1.—Patient (E.H.; J.H.H. No. 401185) 4 months after serum administration showing winging of the right scapula.

ETIOLOGY. The antisera of tetanus, gas gangrene, pneumonococcus, typhoid, diphtheria, meningococcus, gonococcus, scarlet fever and erysipelas have all been reported as producing neurological complications. Tetanus antitoxin is the antiserum most often incriminated. It might be supposed that, along with the other manifestations of serum sickness, the neurological complications may be more common in allergic subjects. Males are more often affected than females probably because of their increased susceptibility to injury and subsequent administration of tetanus antitoxin. In the cases reported it would appear that the

previous administration of serum is not of particular importance, for only 3 of Doyle's 51 cases gave a past history of serum administration[3]. However, symptoms following each of several injections have been reported.

TYPES OF REACTION. The types of reaction can be separated into several groups. Between these groups there may be some overlap. Allen[1] classifies them into central, radicular, neuritic, and polyneuritic. Miller and Stanton[8] separated 100 cases in the literature thus:

Radiculitis, including brachial plexitis (59 cases)	74 cases
Polyneuritis (7) and Guillain-Barré syndrome (3)	10 cases
Landry's paralysis (2) and myelitis (4)	6 cases
Cerebral and meningeal types including optic neuritis (6)	10 cases

The radicular type of case comprises more than 50% and most commonly affected are the 5th and 6th cervical nerves and paralysis of the Erb-Duchenne scapulohumeral type results. Muscles commonly affected are the deltoid, spinati, serratus magnus, biceps, branchialis anticus and triceps; most commonly affected is the serratus magnus. Paralyses have also occurred in the distribution of the musculospiral, the popliteal, the sciatic, the optic and the eighth cranial nerves.

In the central type there may be evidences of meningeal irritation, optic neuritis, cerebral involvement, increased intracranial pressure or localized focal irritation. In looking through Doyle's cases[3] it was noted that optic neuritis appeared to occur in those patients to whom the serum was given intravenously or intrathecally. Serum had been given in a case reported by Cutter[2] in which the patient developed generalized nervous manifestations and a paralysis of the eighth cranial nerve.

DIAGNOSIS. The diagnosis rests largely upon the awareness of the physician to the possibility of this complication following serum therapy and the elicitation of a history of administration of serum prior to the onset of otherwise poorly explained nervous symptoms and signs. These symptoms may arise a few hours to 2 weeks after serum administration but most commonly, especially in the radicular type, from 7 to 10 days.

Difficulty may be encountered when there is no antecedent serum sickness, as the occurrence of this type of complication is not always paralleled by the severity of the serum sickness. Some anticipation of the development of neurological signs may be obtained in patients in whom pain in the shoulders or in the distribution of a nerve or nerve root precedes by several days. This pain may persist for 2 weeks or more. In one of our patients, E.H., it persisted for a month.

Cases bearing a striking resemblance to these radicular complications of serum therapy, and which may be confused with them, are those in which localized neuritis of the shoulder girdle has been associated with other illnesses and in which there has been no administration of serum. In these cases, too, the serratus magnus has been the commonly affected muscle. Spillane[12] and Richardson[10] report a series of such cases. The illnesses have been widely diversified and have included bacillary dysentery (6 cases), influenza, enteric fever, lobar pneumonia, typhus, local and infectious monocucleosis. Richardson reported 5 cases of serratus magnus palsy unassociated with any recognizable disease. It can be seen, therefore, that confronted by one of these diseases and serum administration it may be difficult or impossible to determine whether the paralysis was actually due to the serum. However, the neurology

of the cervical spine is still in a state of flux and many of these cases may be able to be explained later on an anatomical basis.

Differential diagnosis must be made from cervical neuritides from other causes, such as scalenus anticus syndrome and prolapsed cervical disc; also from other conditions, such as progressive muscular atrophy, multiple sclerosis, poliomyelitis, to mention but a few. The complications may mimic many of the peripheral and central nervous system diseases, and the diagnosis must often rest upon careful evaluation of the history.

Examination of the spinal fluid may or may not be of help, as pleocytosis of a mild degree may be found. French workers who studied the spinal fluid in serum sickness without nervous system complications reported a lymphocytosis of 5 to 28 cells per cubic millimeter.

A careful neurological examination of patients with serum sickness may reveal previously unsuspected abnormalities, for it seems unreasonable that the only manifestation would be that of a striking palsy. There must be minor abnormalities that are missed, and in reviewing the 360 cases it was noted that symptoms such as drowsiness, stiff neck, hyperesthesia, anesthesia, and a neuritic type of pain occasionally occurred without apparently any special significance being attached to them, since in most cases they were quite transient. One such patient was a young medical student (JHH No. U 9858) who was given erysipelas antiserum on January 10, 1927, and on January 16 developed a serum reaction with urticaria and generalized glandular enlargement. This reaction subsided with treatment, but on January 18 he developed pains in the calves. The next day he vomited and there were some anesthetic areas described on the arms, and he complained of severe pains in his legs. His symptoms had entirely cleared by January 22.

Two patients have been previously reported from this hospital by Shulman, Schoenrich and Harvey[11], one of whom demonstrated symptoms of sciatic neuritis and the other, cerebral symptoms manifested by drowsiness, lethargy, neck stiffness and muscle weakness.

Nervous system examination may reveal some sensory change but this is not constant. In Doyle's[3] series 25% of the cases of peripheral paralysis demonstrated sensory lesions.

Some of the difficulty encountered in the diagnosis may well be demonstrated in the history of another patient (JHH No. U 74765). This patient had been given antimeningococcal serum for meningococcal meningitis; 6 days later during the convalescent period, he developed serum sickness, manifested by fever, urticaria, pain in the left shoulder and arthralgia. He was given aspirin 0.9 gm. every 2 hours until his ears began to ring and this happened on the first day of administration. Over the next 3 days, although the dose of aspirin was reduced to 0.9 gm. four times a day, he developed severe bilateral nerve deafness. The serum disease abated and the hearing improved considerably during the next 6 weeks. Here there were three possible etiological factors to be considered: meningitis, aspirin therapy and serum sickness. However, the time of onset of the neurological complications is consistent with those arising from serum disease.

PATHOLOGY. The pathology of these complications has not been extensively investigated. Necropsy material has not been abundant. Congestion of the brain, the meninges and the cord, local necrotic areas, demyelinization, glial

and lymphocytic infiltration all have been described. Perivascular edema and infiltration, petechial hemorrhages, edema of the nerves and nerve roots have also been a feature.

Although some writers believe that there may be a direct toxic effect upon the nerve cell and although virus etiology has been postulated, the generally accepted view at present is that changes in the nerve cells are secondary to vascular changes in the nutrient vessels to the nerve, associated with edema of the nerves and nerve roots. The frequency of involvement of the fifth and sixth cervical roots is most likely due to the anatomical arrangement of the dura in the lower cervical region and to the large size of these roots relative to the size of their intervertebral foramina, thus increasing the likelihood of pressure damage. This is an attractive explanation, but one would wonder why the seventh nerve with its long, confined, bony course is not also commonly affected.

As mentioned before, there is a striking similarity between these cases and those seen in the shoulder girdle syndrome described by Spillane[12]. Similar complications and pathological findings have been found in Guillain-Barré syndrome, inoculations with triple typhoid, rabies, dysentery, typhus and yellow fever vaccines.

Miller and Stanton[8] remark that their consideration of the clinical and pathological features of these cases lead them to the belief that these are all manifestations of hypersensitivity. As early as 1935 it was shown by French investigators[6] that repeated injections of foreign protein resulted in perivascular infiltration, cellular destruction in the nervous system and lymphocytic reactions in the meninges. Is the perivascular infiltration, and sometimes hemorrhage, responsible for the change in the nerve cells or is there a direct toxic action upon the cell? Rich[9], also studying the lesions in experimentally produced serum sickness, compared them with those of periarteritis nodosa; one is struck by the similarity between the nervous complications in these two diseases.

TREATMENT. If the nervous system complications are a result of allergic manifestations in the blood vessels and the nerve sheaths, it would certainly seem reasonable that early vigorous therapy with epinephrine and antihistaminics, which reduce the external manifestations of serum sickness, may also have a beneficial effect upon the early nervous symptoms. Once the paralysis is established, this kind of therapy would not appear to be of much use unless there are other signs of active serum disease. It also seems reasonable to suppose that treatment with cortisone or adrenocorticotropin, if instituted early, would be of definite benefit, but there have not been enough cases reported to assess the value of these agents. Shulman, Schoenrich and Harvey[11] report their use in two cases with apparent benefit. In the case reported here, E.H., it may well be argued that cortisone could have been continued longer or reinstated, and this might have prevented some of the complications or might have shortened the convalescence.

For the long term treatment of paralyses, orthopedic and physiotherapeutic measures are of great importance in avoiding permanent deformities.

PROGNOSIS. Except in the rapid anaphylactic central type of reaction, the condition is rarely fatal. Progress may be slow, and while improvement in patients with plexus and single nerve involvement may start in a month, complete recovery may be prolonged and take up to 2 years. According to most

writers about 20% of patients never achieve complete return of function.

Conclusions: A brief discussion of the neurological complications of serum administrations, together with the report of cases from the Johns Hopkins Hospital, has been presented. In a review of 360 patients with severe sickness following administration of various types of antisera, 6 patients with neurological complications were found. Two of these have been presented in some detail and the four others used as examples in the discussion of the problems of diagnosis and management of these complications.

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(Interlingua on page 535)

SUMMARIO IN INTERLINGUA

(See page 541 for original article)

Arrhythmias Cardiac Post Chirurgia Thoracic in Patientes de Etate Avantiate

In nostre dies chirurgia thoracic es recommendate plus frequentemente que antea in le maneamento de patientes de plus que 50 annos de etate, tanto con morbos maligne como etiam con morbos benigne. Post tal chirurgia patientes de tal etates es specialmente susceptibile a disveloppar irregularitates cardiac.

Al Hospital del Universitate de Pennsylvania, 82 patientes de etates de inter 50 e 75 annos esseva subjicite a operationes thoracic durante le periodo ab le 1 de julio 1952 al 1 de julio 1954. Ex le integre gruppo 10 patientes disveloppava un rapide rhythmo ectopic un o plure vices in le curso del periodo postoperative. Isto es un frequentia de 12,2 pro cento.

Iste complication se ha monstrate seriose e pote devenir mortal. Le factores predisponente a arrhythmias cardiac post chirurgia thoracic include le etate del patiente, pre-existente morbo cardiac, arrhythmia antecedente (inclusive le occurentia frequente de contractiones prematur), le natura del lesion chirurgic primari, le extension del intervention chirurgic, anemia, disbalancia electrolytic, e drogas. Le major causas precipitante de arrhythmia es anoxia, reflexos vagal, e hypotension. Nos sublinea le importantia de alertessa, del detection immediate, e de adequate mesuras de tractamento prophylactic e active.

A COMPARISON OF THE HYPNOTIC EFFECTS OF CHLORAL AND ETHINAMATE

By E. L. Foltz, M.D.

Frank Dracos
PHILADELPHIA, PENNSYLVANIA

AND

Charles M. Gruber, Jr., M.D.
INDIANAPOLIS, INDIANA

(From the Department of Medicine and the William Pepper Laboratory of Clinical Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania and the Lilly Laboratory for Clinical Research, Indianapolis General Hospital, Indianapolis, Indiana)

The clinical need for an acceptable, effective, nonbarbiturate agent to produce hypnosis has been long recognized. Recently, several papers[3,4,6,9,10,12] have described such action for 1-ethinyl-cyclohexylcarbamate; this compound is known as "Valamin" in Europe and as "Valmid" (Ethinamate, Lilly) in the United States. In comparison with the barbiturate, Secobarbital Sodium, its hypnotic effects appeared as satisfactory but of shorter duration of action than Secobarbital[5]. It became important to assess whether this agent possessed attributes more desirable than other nonbarbiturate agents. A comparison with chloral forms the basis for this report. Chloral alcoholate was chosen because of its solid state which permits incorporation in capsule form; the use of capsules made possible "double-blind" studies in which chloral as well as placebos were administered. Chloral alcoholate has been previously shown to possess activity identical to that of the hydrate[1].

Two independent studies were simultaneously undertaken to define its action in comparison with chloral. One study (A) required active observation of the patient and his participation in performance studies. The other study (B) was based on passive participation and subjective reporting by the patient.

STUDY A: ACTIVE OBSERVATION STUDIES. **Method.** Ten hospitalized patients with various medical diagnoses were used. Two patients at a time were segregated in a relatively quiet, two-bed room. Each night at bedtime, one patient received an oral dose of Ethinamate and the other patient received the same weight dose of chloral alcoholate. On the first and second nights, 1.0 gm. of each drug was given, so that each patient received one dose of each drug. On the third and fourth nights, 1.5 gm. of the drugs were given and for two nights 2.0 gm. were given. Before the drugs were given and hourly for at least 6 hours afterward, the depth of central nervous system depression was estimated and the blood pressure, pulse and respiratory rates were determined. These estimates and determinations were made by nurses. A "double-blind" testing procedure requiring identical capsules of the two drugs was used.

The following criteria defined the central nervous system effects: 1) "Sleepiness is the desire to go to sleep, but the ability to stay awake without effort. No change in the heel-to-knee-to-toe and normal speech are present. 2) Lethargy is the ability to stay awake with effort. Ataxia and slow speech are present. 3) Stupor is the presence of a response to painful stimuli. Inability to perform the heel-to-knee-to-toe test, and slurred and confused speech are observed. 4) Coma is present when moderately intense painful stimuli, such as supra-orbital pressure, does not arouse a response." Occasionally the nurse's reports were checked by a physician or by giving placebo

capsules. The two drugs were always given in equal doses, one to each of the 2 patients, as four identically appearing capsules.

Results. The means of the control blood pressures, pulse, and respiratory rates, and the means of the extremes for each of these during the testing period were determined as in the previous paper[5]. No change was seen in any patient which was clinically significant. Statistical analysis of the data was not carried out for this reason.

The number of patients developing each intensity of central nervous system effect is recorded in Table 1. The method of Litchfield and Wilcoxon[7] was used to determine equieffective doses of the two drugs (Fig. 1). The row totals indicate the number of positive responses. The maximum number of positive responses for all 4 intensities of central nervous system depression would occur if all patients developed coma. In this case, there would be 40 positive responses. The per cent probabilities were determined by dividing the row totals by the maximum (40). From this data, the ED_{50}'s for Valmid (Ethinamate) and for chloral alcoholate were found to be 1.4 and 2.0 gm., respectively. The two lines are significantly different ($p = 0.01$) when examined by the Sign test[8] and combined probabilities[2].

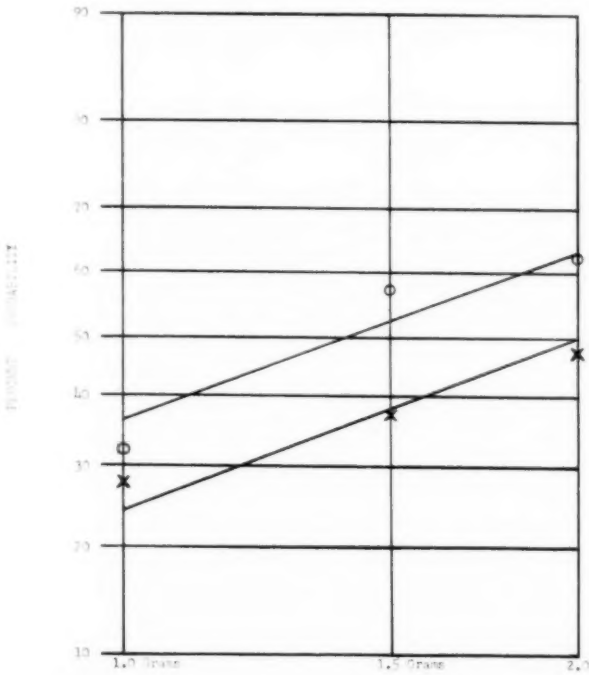

Fig. 1.—A figure in which the per cent probability is plotted against the log of the dose according to the method of Litchfield and Wilcoxon[7]. The open circles and upper line are for Valmid, the crosses and lower line for chloral alcoholate.

The time lapse between the administration of the drugs and the development of central nervous system depression of the various intensities is approximately the same for the two drugs. Valmid did produce depression more

TABLE 1.—EACH OF 10 PATIENTS RECEIVED ORAL DOSES OF VALMID OR CHLORAL ALCOHOLATE. ESTIMATES WERE MADE OF THE MAXIMUM CENTRAL NERVOUS SYSTEM DEPRESSION OCCURRING. THE NUMBER OF PATIENTS DEMONSTRATING EACH INTENSITY OF EFFECT ARE RECORDED.

	Sleepy		*Lethargic*		*Stuporous*		*Comatose*		*Row Totals*	
Dose in gm.	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*
1.0	9	8	4	3	0	0	0	0	13	11
1.5	10	10	9	5	3	0	1	0	23	15
2.0	10	10	10	5	3	3	2	1	25	19
Column Totals	29	28	23	13	6	3	3	1	61	45

TABLE 2.—PRESENTING THE NUMBER OF HOURS THAT CENTRAL NERVOUS SYSTEM DEPRESSION OF A GIVEN INTENSITY (OR GREATER INTENSITY) PERSISTED. THE TOTALS FOR THE 10 PATIENTS ARE RECORDED

	Sleepy		*Lethargic*		*Stuporous*		*Comatose*		*Row Totals*	
Dose in gm.	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*	*Valmid*	*Chloral Alcoholate*
1.0	40	35	15	11	0	0	0	0	55	46
1.5	56	45	36	12	6	0	3	0	101	57
2.0	62	54	46	28	13	4		2	127	98
Column Totals	158	134	97	51	19	14	9	2	283	201

quickly than did chloral alcoholate (Sign test[8] and combined probabilities[2], $p = 0.05$), but this does not seem to be clinically significant.

The sums of the durations of the central nervous system effects of the drugs are presented in Table 2. These data were obtained in such a way that all periods of depression of lesser intensity include the number of hours of greater intensity. For example, the number of hours of lethargy with a given dose of either drug includes all of the hours during which stupor was observed in that series of estimates. From this table it is obvious that gram for gram Valmid has a longer duration of action than does chloral alcoholate. (Sign test[8] and combined probabilities[2], $p = 0.05$).

The row totals from Table 2 were plotted on the ordinate and the doses of the drug on the abcissa of log-log paper (Fig. 2). These row totals are equivalent to the total score which would be obtained if each hour during which sleepiness, lethargy, stupor, or coma were specifically observed, was scored as 1, 2, 3, and 4, respectively.

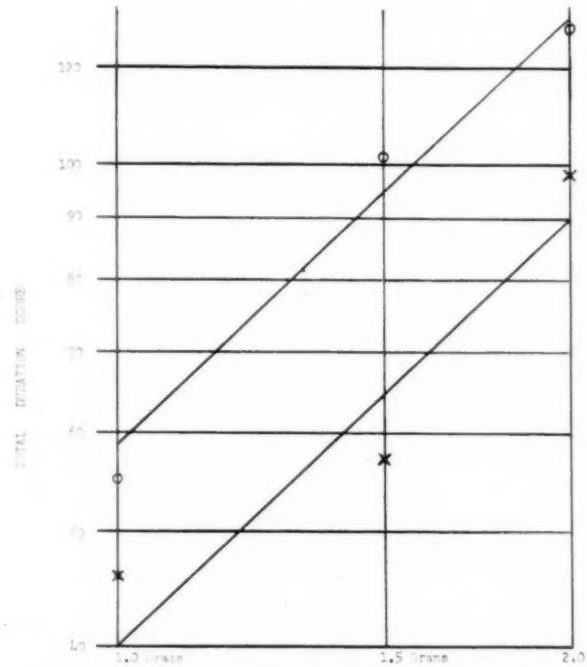

Fig. 2.—A figure in which the log of the total duration score is plotted against the log of the dose in gm. The open circles and upper line are for Valmid, the crosses and lower line for chloral alcoholate.

From this figure, it is possible to determine doses of Valmid and chloral alcoholate which have approximately the same duration of action. The doses which would be expected to produce a duration score of 80 (DS_{80}) are 1.3 and 1.8 gm. for Valmid and chloral alcoholate, respectively.

STUDY B: PASSIVE PARTICIPATION AND SUBJECTIVE REPORTING STUDIES. **Methods.** Patients with cardiac, pulmonary, gastroin-

testinal, genitourinary, endocrine, ophthalmologic, and infectious disorders were used. They were chosen out of the mild and moderately ill groups on the basis of their needs for drugs to induce sleep and their ability to give intelligent answers to questions concerning the effects of drugs. Each subject was rotated in a random fashion through nightly administration of identical capsules containing either chloral alcoholate, Ethinamate, or placebo. Each capsule contained 250 mg. of the respective agents. Doses of the active drugs were 0.5 gm. in the first group of subjects and 1.0 gm. in the second group; similar numbers of capsules of the placebo were given to match the current doses of the active drugs. Two or more patients were followed simultaneously on each ward; the order of drug administration was randomized so that on any given night at least 2 or perhaps all 3 preparations were used on each ward. In this fashion, an attempt was made to minimize the bias produced by the unavoidable interruptions of sleep which are bound to occur on hospital wards. The medications were taken at a uniform hour each evening, subjects were frequently wakened by ward staff members for morning care before the patients had completed their sleep.

The patients were interviewed each day of the study. Neither the examiner nor the patient knew the nature of the medication for the previous night. At the completion of each dosage group, decoding and appropriate tabulation of the data were carried out. Statistical evaluation of differences between results with the three agents was accomplished by the Chi-square test[8].

TABLE 3.—PRESENTING THE PATIENTS' ESTIMATES AS TO THE QUALITY AND QUANTITY OF SLEEP OBTAINED AFTER TAKING 250 OR 500 MG. OF CHLORAL ALCOHOLATE OR ETHINAMATE AT BEDTIME.

	Quality of Sleep			*Quantity of Sleep*			
Two Capsules	*Good*	*Intermediate*	*Poor*	*Onset in Minutes*	*Duration in Hours*	*Interruptions*	*Dream*
Placebo	10	5	4	64	7.4	36	6
Chloral	15	2	2	55	7.6	38	0
Ethinamate	17	1	1	44	7.7	16	0
Four Capsules							
Placebo	21	4	7	97	6.9	69	8
Chloral	22	3	7	77	7.7	60	9
Ethinamate	28	2	2	58	7.7	34	8

TABLE 4.—SYMPTOMS AND SENSATIONS OBSERVED BY THE PATIENTS ON AWAKENING

	Two Capsules			*Four Capsules*		
	Placebo	*Chloral*	*Ethinamate*	*Placebo*	*Chloral*	*Ethinamate*
Mental obtundity	3	6	2	8	7	7
Weakness	2	0	0	1	0	0
Fatigue	6	8	3	1	9	7
Sweating	2	1	3	0	1	1
Headache	2	8	3	5	6	3
Nausea and heartburn	0	2	1	3	2	2
Abdominal cramps	1	1	0	2	2	1
Malaise or pain	2	2	1	6	2	2
Dizziness	0	3	1	3	6	4
Restlessness	1	2	0	11	7	4
Nervousness	0	0	1	0	0	0
Anxiety	1	0	1	2	4	0
Totals	20	33	15	42	46	31

Results. The estimates of the effectiveness of the medications are presented in Table 3. Analysis of the data as a whole demonstrated a significant

difference in the quality of the rest produced by the drugs ($p<0.05$). When compared to placebo, Ethinamate produced a significant increase in the number of patients reporting improved quality of sleep ($p<0.01$) whereas chloral did not ($p> 0.10$). The onset of sleep was more prompt with Ethinamate than with either placebo or chloral. The small increase in duration with Ethinamate is directly proportional to the decrease in the interval for the onset of sleep since most patients were wakened at the same hour for morning care. The distribution among the medications of the interruptions of sleep was significant when individual doses or all of the data was considered ($p<0.001$). The principal contribution to this heterogeneity was produced by a decrease in the frequency of disturbance when Ethinamate was given.

The incidence of undesirable side-effects is shown in Table 4. The distribution appears significant ($p<0.05$) for the 0.5 gm. dosage and when both doses are combined for statistical analysis. The main feature of this variation was the greater number of symptoms reported for chloral alcoholate than for Ethinamate.

Discussion. The evaluation of the hypnotic effects of a drug is beset with many difficulties. Objective tests either require mental activity of the patient or actual physical participation; both of these procedures may modify or interfere with the hypnotic action. Subjective phenomena as reported by the patients or subjects are open to criticism that the interpretation and importance of certain experiences may be inaccurately reported. A double evaluation in which both of these objections can be weighed against the results constitutes in our opinion the most objective appraisal of the hypnotic actions of drugs. Furthermore, the use of a "double-blind" technique removes the bias inherent in working with any new promising agent.

Ethinamate demonstrated effective hypnotic activity in both studies. Both groups noted onset of drug action within 30 to 60 minutes; a shorter interval between ingestion of drug and the onset of sleep was noted for Ethinamate than for chloral. It was also noted in Study B that both active agents were more rapid for onset of sleep than was the placebo.

In Study B, patients confined to bed responded in more rapid fashion to the hypnotic effects of drugs. Ambulatory patients who had slept or rested during the day, frequently chose to spend time in the ward day-room watching television after evening medications had been given; occasionally, sleep overtook these patients before they had retired to bed.

The estimated effective doses as determined in Study A are smaller for Ethinamate. Dose-effect data may certainly be used as a measure of the intensity of drug action. Usually a single endpoint is involved. In this experiment, 4 endpoints were used. The authors believe that the composite data could be represented by the usual sigmoid curve. Therefore, the use of this data does not invalidate the conclusions, but produces a more accurate estimate of the response of the patients to the drugs.

With most central nervous system depressants, the log of the duration of effect is proportional to the log of the dose. For this reason it was assumed that parallel straight lines were the proper curves to be obtained for these drugs in Fig. 2.

When an attempt is made to compare doses (by means of the curves) with equal effectiveness or equal durations there appears to be no difference between the two drugs; however,

Ethinamate is about half again as active as chloral alcoholate on equal dosage. Chloral alcoholate is of equal potency to that of chloral hydrate[11]; this same ratio (1.5) of activity should hold for Ethinamate and chloral hydrate.

Qualitatively, Ethinamate was followed by deeper sleep than was chloral. This was apparent in the grading of intensity response in Table 2 (Study A) and by the lower frequency of interruptions to sleep shown in Table 3 (Study B). Other differences which marked the superiority of Ethinamate were the lower incidence of side effects associated with the hypnotic effects, and at the same time, the less frequent persistence of symptoms of disease processes that interrupted or interfered with sleep. Whereas fatigue and mental obtundity (dullness, sluggishness) were frequently observed after chloral alcoholate, these symptoms occurred with Ethinamate only when the heavier dosage was used and then, only, in low frequency. Headaches were least frequent in association with Ethinamate. Restlessness and malaise or pain which were prominent in the group receiving the larger doses in Study B, seemed to be more effectively allayed by the use of Ethinamate. A sensation of anxiety while insomnia existed was more commonly encountered after chloral therapy.

Gastrointestinal irritation was noted in a few cases, but occurred more frequently in those patients on chloral therapy.

In general, the results of both studies point to the superiority of Ethinamate over chloral alcoholate in regards to the hypnotic actions. One cannot ignore that similar conclusions have been formulated as the result of two independent studies which were widely separated geographically, and which employed both subjective and objective observations as the bases for the data presented.

Summary. Ethinamate is an effective agent for hypnosis.

It appears to be 1.5 times as effective as chloral alcoholate on a dose weight basis.

Its administration is followed by a more rapid although probably not clinically significant onset of sleep than noted after chloral.

The duration of action of Ethinamate is relatively short, but appears to be longer than that for chloral on an equal weight basis.

Ethinamate was followed by more restful sleep, fewer interruptions and the lower incidence of side effects when compared to chloral alcoholate.

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SUMMARIO IN INTERLINGUA

Comparation del Effectos Hypnotic de Chloral e Ethinamato

Ethinamato (cognoscite in Europa como Valamina) es un efficace agente hypnotic. Illo pare esser 50 pro cento plus efficace que alcoholato de chloral. Doses de equal efficacia del duo drogas ha pesos del proportion de 2 a 3.

Le administration de Ethinamato es sequite per un plus rapide advenimento de somno que le administration de chloral. Iste differentia es probabilemente sin signification clinic.

Le duration del effectos de Ethinamato es relativemente breve sed illo pare esser plus longe que le duration del effecto de un dose del mesme peso de chloral.

Le somno producite per Ethinamato es plus quiete e plus continue que le somno producite per alcoholato de chloral. Etiam le effectos lateral de Ethinamato es minus frequente.

SUMMARIO IN INTERLINGUA

(See page 520 for original article)

Complicationes Neurologic Post le Administration de Seros

Le protocollos de 360 patientes interne, tractate al Hospital Johns Hopkins a Baltimore pro morbo seral, esseva studiate. Il esseva constatate que le serie total includeva 6 casos de complicationes neurologic. Duo de iste casos es describite in detalio; le alteres es mentionate brevemente in le discussion del diagnose e del tractamento de complicationes del genere mentionate.

Un del casos describite in detalio esseva le caso de un juvene homine qui disveloppava ataxia post le administration de sero como tractamento de raucitate del gurgite. Le ataxia esseva accompaniate per un certe grado de dolor del articulationes. Un transiente eruption maculate habeva occurrite. Varie diagnoses esseva considerate: febre rheumatic, periarteritis nodose, lupus erythematose, e multiple sclerosis. Le revista del curso del maladia, su symptomatologia, e le facto que 14 annos plus tarde le patiente se trovava ben pare indicar que le ataxia representava un manifestation neurologic de morbo seral.

Le secunde del casos describite in detalio esseva le caso de un juvene femina qui suffreva de sever morbo seral post reciper sero antidiphtheritic. Al initio le morbo seral esseva tractate conservativemente per antihistaminicos e ephedrina. Plus tarde large doses de cortisona esseva usate, sed istos non succedeva a prevenir le disveloppamento de un sever paralyse del cinctura dextero-scapular. A grado reducite iste paralyse persisteva ancora 6 menses post le declaration del morbo. Un complication additional del morbo seral esseva un non-granulomatose uveitis.

Il es postulate que un exacte examine neurologic de casos de morbo seral va possibilemente revelar signos neurologic intra 2 septimanas post le administration del sero, specialmente in patientes con dolores scapular o con dolores in distribution nerval.

In casos con complicationes neurologic il pare recommendabile applicar un therapia steroide le plus promptemente possibile.

HYALURONIDASE AND RENAL CALCULI IN POLIOMYELITIS

By J. R. Taylor, M.D.
CONSULTANT IN UROLOGY, WINNIPEG MUNICIPAL HOSPITALS, AND
DEPARTMENT OF UROLOGY, WINNIPEG CLINIC

A. J. W. Alcock, M.D.
ACTING MEDICAL DIRECTOR, WINNIPEG MUNICIPAL HOSPITALS

AND

J. A. Hildes, M.D.
ASSOCIATE PROFESSOR, DEPARTMENT OF PHYSIOLOGY AND MEDICAL RESEARCH,
UNIVERSITY OF MANITOBA
FORMER MEDICAL DIRECTOR, WINNIPEG MUNICIPAL HOSPITALS

(From the Winnipeg Municipal Hospitals, Winnipeg, Manitoba, Canada)

The administration of hyaluronidase for the prevention of recurrent renal calculi was introduced by Butt in 1952[1]. Based on the observation that a subcutaneous injection of hyaluronidase increased the "colloidal activity" of urine[2,3,4,10,13], Butt found that recurrent stone formers have a deficiency of "protective colloids" in the urine. He considered that this deficit could be corrected by the use of hyaluronidase.

Our experience with severely paralyzed poliomyelitis patients in respirators for over 6 weeks agrees with reports in the literature on other long-term recumbency states[9,11], in that a high proportion (28% of our cases) formed renal stones. Clinically and radiologically these resembled calcium phosphate stones. Because of this serious complication, together with favorable reports concerning the prophylactic value of hyaluronidase, we contemplated treating all such cases with this drug. However, as the efficacy of this treatment was not firmly established, it was considered important to study a concurrent series of control patients. To our knowledge such a control series had not been previously reported.

Materials and Methods. During 1952 and 1953 the Winnipeg Municipal Hospital served as the main treatment center for poliomyelitis in Manitoba. A total of more than 1300 acute cases were admitted. Of these, 227 required respirator treatment. By April, 1954, when this study was undertaken, 59 chronic respirator cases remained in the hospital. Table 1 shows the patients studied with reference to their age and sex distribution. There was a predominance of males over females, in keeping with the increased incidence of the disease in males. The age range was from 2 to 65 years, although the majority of patients were young adults. As there is a racial difference in the incidence of renal calculi[8], it is to be noted that all patients in this study were white. The interval between the onset of poliomyelitis and this study ranged from 2 to 21 months, with an over-all average of less than 8 months.

Urine retention in this series of severely paralyzed patients was a common complication during the early stages of their poliomyelitis. All but three of the patients required indwelling catheters for varying periods ranging from a few days up to 4 months, with an average of 4 weeks. Although none of the patients required catheters during the trial, a pre-existing pyuria from previous catheter treatment in many of the patients made it difficult to recognize a low-grade infection of the upper urinary tract.

The trial was conducted over a 7-month period. The presence of renal calculi as well as changes in number, size and position, was determined by Roentgen-ray examination carried out at the beginning of, and at regular intervals throughout the trial. Because of

accumulation of gas and feces, plain films of the abdomen were not always satisfactory, particularly early in the trial when films could be obtained in some patients only by portable technique in the respirator. By persistent attempts to obtain satisfactory films in doubtful cases the presence or absence of calculi and their size and position were established in all cases with satisfactory certainty, albeit only in retrospect in some cases. For technical reasons, excretory and retrograde pyelograms were not used routinely.

After the initial radiological survey the patients without stones were divided by random chance into a group for hyaluronidase treatment and a control group. With the exception of 4 patients who were used as a small control group, all patients with stones were given the benefit of hyaluronidase treatment. At the end of the survey the careful re-appraisal of all films made reclassification necessary in 5 patients. Seven of the original patients were dropped from the study for such reasons as operative removal of stones or early ambulation.

All patients were treated alike with regard to diet, fluid intake and activity. The trial was not allowed to interfere with routine treatment of their residual paralysis and, therefore, some patients attained independence of their respirators and increased activity faster than others, but it was hoped that these individual differences would be equally spread throughout the groups. Records were maintained of the daily urine volume (but not of pH), the time spent in the respirator, and of various forms of activity, particularly the use of the rocking bed, wheelchairs and standing boards[5].

All patients were placed on diets calculated to contain less than 1 gm. of calcium per day. No attempt was made to prevent the intestinal absorption of calcium by the use of phosphorus-binding agents.

The treated patients were given daily subcutaneous injections of hyaluronidase in sufficient dosage to clear the urine of turbidity, after the method of Butt[2]. The dose was adjusted by daily examination of the urine and averaged 850 turbidity reducing units, with a range of 300 to 1500.

Results. It can be seen from Table 2 that in the group without pre-existing stones, out of the 12 patients (Group I) who received hyaluronidase, one developed a renal calculus. In the 22 controls (Group II), 4 of the patients developed renal calculi. Details of each of these patients are listed in Table 3.

In the group with pre-existing stones, 9 of the 14 treated with hyaluronidase (Group III) showed an increase in stone formation. There was also an increase in stone formation in 2 of the 4 untreated patients (Group IV). As might be expected, statistical analysis revealed no significant difference between Groups I and II and between Groups III and IV.

An attempt was made to maintain a high urine output on all patients and to record these daily. Of a total of over 11,000 patient-days, records were not available for 15%. This was mainly due to the transfer of a few patients to a convalescent ward where output records were not kept. There was no appreciable difference in output between Groups I, II, III and IV; nor was there any difference between the

TABLE 1. DISTRIBUTION OF PATIENTS

	Group	*Average Age*	*Sex*
Without Stones	I (on hyaluronidase) 12 cases	27.4 years Range 2–65	5 female 7 male
	II (control) 22 cases	26.8 years Range 7–39	7 female 15 male
With Stones	III (on hyaluronidase) 14 cases	28.3 years Range 9–38	8 female 6 male
	IV (control) 4 cases	29.8 years Range 27–35	0 female 4 male

16 patients who developed new or larger stones and the 36 patients who showed no change (Table 4). Similarly, those patients who developed stones appeared to spend as much time on the rocking bed and standing board as the other patients, although records are not sufficiently detailed to permit statistical analysis.

No untoward effects from the daily injection of hyaluronidase were observed.

Discussion. In evaluating the various possible factors contributing to stone formation in this type of patient, the common association of recumbency with kidney stones implies an etiological relationship. Although the tendency for stagnation is one factor, the widespread demineralization resulting from immobility, leading to a high urinary calcium output, is undoubtedly of greater importance. It is interesting to note that the 5 patients who developed stones for the first time during the trial, did so after from 7 to 9 months of immobility. It seems reasonable to expect stones to form earlier while demineralization and hypercalcinuria are maximal, with a progressively lower incidence of stone formation with the passage of time. It has been shown

TABLE 2.—RESULTS

		Total	*No Change*	*New Stone**
Treated with hyaluronidase	Group I (No stones)	12	11	1
	Group III (Pre-existing stones)	14	5	9
Controls	Group II (No stones)	22	18	4
	Group IV (Pre-existing stones)	4	2	2

* Either increase in size of pre-existing stones, new stone formation, or both.

TABLE 3.—PATIENTS DEVELOPING STONES DURING THE TRIAL

Case No.	*1*	*2*	*3*	*4*	*5*
Sex and age	Female: 14	Male: 20	Male: 39	Male: 27	Male: 21
Interval between onset of polio and visualization of renal stone	9 months	8 months	14 months	9 months	11 months
Extent of paralysis	Paraplegic, free of respirator after 11 months	Tetraplegic, out of respirator 4–6 hours a day	Tetraplegic, full time respirator	Tetraplegic, out of respirator 5–6 hours a day with 'frog-breathing'	Tetraplegic, out of respirator 12 hours a day
Indwelling catheter	31 days	28 days	14 days	22 days	7 days
Hyaluronidase, average daily dose	600 T.R.U.	None	None	None	None
Urine Volume During Trial					
Less than 1000 cc.	48 days	7 days	47 days	23 days	50 days
Between 1000–1500 cc.	114 days	34 days	85 days	55 days	87 days
Over 1500 cc.	44 days	179 days	88 days	135 days	78 days
Unrecorded	14 days	0	0	7 days	5 days

by Freeman[7] that hypercalcinuria due to immobility is a continuous process until ambulation is restored.

Realizing that restoration of muscle power may be a slow and incomplete process in poliomyelitis, various measures have been devised to substitute for movement and weight bearing. Although we have not attempted a study of calcium excretion in our patients, the clinical results recorded show that passive substitutes for ambulation, namely, rocking bed and standing board, did not completely prevent the development or growth, or both, of kidney stones. Whether it has prevented a higher incidence of this complication it is impossible to say. Wyse and Pattee[12] found that the tilt board was without effect on calcium balance of early paraplegics.

However, it was felt that the resultant changes in position brought on by the standing board and rocking bed do play an important role in the passage of small and medium-sized stones and, for that reason, we believe them to be important therapeutic procedures in the management of renal calculi in paralyzed patients.

The production of a dilute urine should be an additional safeguard against the precipitation of calcium salts in the kidney and renal pelvis. Urine volumes of 1 to 2 liters per day did not prevent stone formation in these cases.

The employment of an agent to prevent the precipitation of calcium salts would appear to be a fundamentally sound approach to this difficult problem. Unfortunately the results of our survey indicate that hyaluronidase in the doses we employed neither completely prevented the growth of pre-existing stones nor the appearance of a new stone in one case. These findings are in agreement with those of others[6]. Whether it curtailed such growth and prevented additional patients from showing stone formation it is not possible to say, but it would appear to have been of little or no significant value in the management of these patients.

TABLE 4.—RECORDED URINE VOLUME IN PATIENT-DAYS*

Urine Volume	*16 Patients with Increase or New Stone Formation*	*36 Patients with No New Stone Formation*
Over 1000 cc.	77%	77%
Over 1500 cc.	44%	50%

* 15% of urine volumes were unrecorded.

Summary. 1. Fifty-two chronic respirator cases were studied for 7 months to assess the value of hyaluronidase treatment in the prevention of new or additional renal stone formation.

2. Of the cases without stones at the beginning of the trial, 12 were treated with hyaluronidase injections daily and 22 served as controls. Stones developed in one of the treated and 4 of the untreated cases.

3. Of 18 patients with stones at the beginning of the trial, 14 were treated with hyaluronidase. Of this group, 9 showed an increase in size or number of stones or both. Two of 4 untreated control patients with pre-existing stones showed an increase in size or number of stones, or both.

4. Although it cannot be definitely stated that hyaluronidase had no effect on the patients treated, it seems unlikely that the treatment was of practical benefit.

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SUMMARIO IN INTERLINGUA

Hyaluronidase e Calculos Renal in Poliomyelitis

1. Esseva studiate durante 7 menses un serie de 52 casos chronic de poliomyelitis sub tractamento a pulmon de aciero. Le objectivo del studio esseva determinar le valor del tractamento a hyaluronidase in le prevention del formation de nove o addite calculos renal.

2. Al comenciamento del studio 34 casos sin calculos esseva dividite in duo gruppos: 12 recipeva injectiones diurne de hyaluronidase e 22 serviva de controlo. Un del patientes tractate e 4 del patientes non-tractate disveloppava calculos.

3. Ex le gruppo de 18 patientes con calculos al comenciamento del studio, 14 esseva tractate con hyaluronidase e 4 non. Inter le patientes tractate, 9 monstrava un augmento del numero o del dimensiones del calculos o ambes. Inter le 4 non-tractate patientes de controlo, 2 monstrava un augmento del numero o del dimensiones del calculos o ambes.

4. Ben que il non es possibile asserer categoricamente que le tractamento habeva nulle effecto super le patientes, il non pare evidente que hyaluronidase esseva de valor practic.

CARDIAC ARRHYTHMIAS IN THE OLDER AGE GROUP FOLLOWING THORACIC SURGERY

By Arthur Krosnick, M.D.*
ASSISTANT INSTRUCTOR IN MEDICINE, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

AND

Fred Wasserman, M.D.
RESEARCH FELLOW, HEART ASSOCIATION OF SOUTHEASTERN PENNSYLVANIA

(From the Department of Medicine and Division of Cardiovascular Diseases, The Graduate Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania)

Thoracic surgery is now being offered more frequently to the patient over 50 years of age, for both benign and malignant diseases[1,10,27,29]. Evaluation of elderly patients by the anesthesiologist, surgeon and internist requires alertness directed toward operative and postoperative morbid states peculiar to this age group[1,7,13,14,27,29,31]. In recent years, we have been particularly impressed by the fact that patients in the sixth decade, and beyond, are especially prone to develop irregularities of the heart beat following operations on the chest. Ectopic rhythms in the older age group of patients are often serious and may be fatal[2,9,22].

The purpose of this paper is to evaluate the incidence of this problem and the contributing factors, and to discuss the prophylactic and active treatment.

Method of Study. Ten cases of cardiac arrhythmias in the older age group (50 to 74 years of age) followed thoracic surgery at The Graduate Hospital of the University of Pennsylvania between July 1, 1952, and July 1, 1954. The data were analyzed regarding the age and sex of the patient, preoperative cardiac status, type of operation, the approximate time of onset and kind of arrhythmia following the surgery, mortality and the results of treatment. The significant findings are recorded in Tables 1 to 5. Most of these cases were treated during the period of hospitalization by the authors.

Case Reports. Note: All ventricular rates during the period of ectopic rhythms ranged between 150 and 220 per minute (from the electrocardiograms). The case histories are intentionally brief. The signs and symptoms observed at the time of detection of the arrhythmia included dyspnea, which was often severe, anxiety, palpitation, diaphoresis, hypotension and pulmonary edema. None of the patients complained of substernal oppressive or crushing precordial chest pain; the chest pain frequently described was related to the operative wound.

Case 1. I. O., a 71-year-old white male, had a left pneumonectomy for epidermoid carcinoma. He had no previous cardiovascular symptoms, and had a good exercise tolerance. The examination of the heart was negative; the blood pressure 144/80. A preoperative electrocardiogram demonstrated a normal sinus rhythm, with occasional premature auricular and ventricular contractions, and changes suggestive of an old posterior myocardial infarction. On the first postoperative night, the patient developed paroxysmal auricular fibrillation (Fig. 1), with a ventricular rate of 165/minute. He was treated with a lanatoside-C preparation intravenously, and in 5 hours reverted to sinus tachycardia with a rate of 105/minute. The rhythm was regular until the eighth postoperative day, when he developed a paroxysmal auricular flutter fibrillation, with a ventricular rate of 135/minute. After the administration of additional digitalis he developed auricular fibrillation and then reverted to a normal sinus rhythm with a rate of 90/minute. Occasional prema-

*Present address: 383 West State St., Trenton, N. J.

ture ventricular contractions remained until he was discharged.

CASE 2. R. B., a 60-year-old Negro male, was admitted with weakness, cough, dyspnea, and roentgenographic evidence of a pulmonary mass. The cardiovascular history was negative. Examination of the heart was negative; the blood pressure was 130/80. A preoperative electrocardiogram showed only diminished T-wave amplitude. The patient had a left pneumonectomy for squamous cell carcinoma arising in a bronchus. On the fifth postoperative day, he had an episode of hypotension (80/65) associated with a paroxysmal auricular flutter with a 2:1 ventricular response (ventricular rate 150/minute). He was digitalized with lanatoside-C, and reverted to a normal sinus rhythm in 8 hours. On the seventh postoperative day, he again developed paroxysmal auricular flutter (with a 2:1 ventricular response). He was re-digitalized with intravenous lanatoside-C, and within 8 hours returned to sinus rhythm, which remained until discharge.

CASE 3. I. B., a 67-year-old Negro male, was admitted for investigation and treatment of a pulmonary condition, characterized by repeated pneumonias, cough, hemoptysis, weight loss, and the like. There were no cardiac symptoms. The heart was normal in size; blood pressure 150/90. A grade 1 aortic systolic murmur was heard. A left upper lobectomy was performed for epidermoid carcinoma. A preoperative electrocardiogram was normal. On the first postoperative day, the patient developed a sinus tachycardia with frequent auricular and ventricular premature contractions. On the second postoperative day, he was found to have auricular flutter, with a 2:1 ventricular response, with a ventricular rate of 150/minute. He was rapidly digitalized parenterally with Digoxin, and the rhythm converted to auricular fibrillation, and then to a normal sinus rhythm within 7 hours. On the third postoperative day, the rhythm was sinoauricular with frequent premature auricular and ventricular contractions. On the fourth postoperative day, however, the patient was again in auricular fibrillation. He was given additional digitalis and reverted to sinus rhythm with occasional premature contractions. The patient was

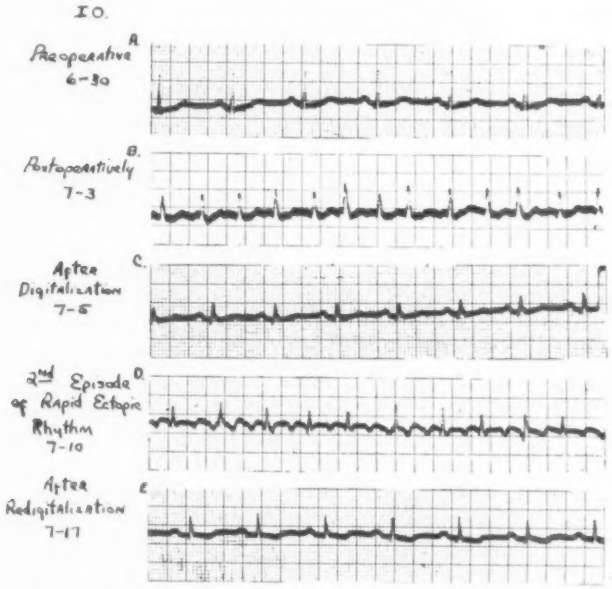

Fig. 1.—Electrocardiograms (Lead II), showing: *A*. Preoperative tracing; normal sinus rhythm with a rate of 80/minute, *B*. Postoperative auricular fibrillation, with a rate of approximately 165/minute, *C*. Conversion to sinus tachycardia with a rate of 105/minute. *D*. Return of arrhythmia with a ventricular rate of 135/minute (flutter-fibrillation), *E*. Conversion to normal sinus rhythm; rate 90/minute.

started on quinidine gr. iii, Q.I.D., and the premature ventricular contraction disappeared prior to discharge.

CASE 4. J. R., a 67-year-old white male, with a previous history of a perforated gastric ulcer, was admitted with a massive upper gastrointestinal hemorrhage. The bleeding stopped promptly, and in the course of study, the patient was found, by Roentgen ray, to have a pulmonary lesion. He denied previous cardiovascular symptoms or disease, but on physical examination, he was found to have a grade I systolic and a grade I diastolic aortic murmur with a suggestive systolic aortic thrill and an absent A2. There was slight left ventricular enlargement and dilatation and elongation of the aorta. His blood pressure was 110/80. Electrocardiogram showed a sinus rhythm with occasional premature ventricular contractions and a pattern suggestive of left ventricular hypertrophy. The mass in the lung proved to be an epidermoid carcinoma originating in a bronchus, and a right pneumonectomy was performed. On the third postoperative night, the patient went into acute left ventricular failure with pulmonary edema. He was rapidly digitalized with intravenous lanatoside-C and received other standard treatment (tourniquets, oxygen, and the like). Within 3 hours, he was much improved, but 7 hours later the patient went into a state of peripheral vascular collapse, and electrocardiographically was found to have ventricular tachycardia (rate 180/minute). He failed to respond to intravenous procaine amide and expired. Postmortem examination revealed calcific aortic stenosis, dilatation of all cardiac chambers, left ventricular hypertrophy, pulmonary congestion and edema.

CASE 5. S. S., a 50-year-old white male, with a long history of duodenal ulcer disease was admitted for re-evaluation. Because of a chronic cough, a chest roentgenogram was taken and it revealed a mediastinal mass. There was no previous cardiovascular symptomatology except that the patient told of three episodes of paroxysmal rapid heart beat, which lasted about one hour each and which stopped spontaneously. The precise type of arrhythmia was unknown. Examination of the heart was negative; blood pressure was 134/76, pulse 72/minute. Electrocardiogram showed nonspecific T wave changes with a normal sinus rhythm. A left pneumonectomy was performed for a bronchiogenic carcinoma which had invaded the left pulmonary artery. Accordingly, it was necessary to resect the left vagus and left recurrent laryngeal nerves. On the third postoperative day, the patient developed paroxysmal auricular fibrillation, with a ventricular rate of 214/minute. He was rapidly digitalized with intravenous lanatoside-C, and reverted to a normal sinus rhythm with frequent premature auricular contractions. On the fourth postoperative day, he again developed paroxysmal auricular fibrillation, which responded to additional doses of Digoxin. On the fifth postoperative day, he developed a third episode of paroxysmal auricular fibrillation, and once more responded to additional digitalis. He remained in a normal sinus rhythm from this time until discharge, having received 2.6 mg. of Cedilanid, 1.5 mg. of Digoxin and 1 cat unit of Digalin in aproximately 48 hours.

CASE 6. J. J. S., a 68-year-old white male, was admitted with complaints of cough and dyspnea. He stated that a shadow was found by chest roentgenogram 40 years before admission, and again 4 years prior to admission. There were no symptoms of congestive heart failure, except for dyspnea and physical examination was unremarkable. Blood pressure was 110/70. The patient was digitalized preoperatively, but there was no improvement in the dyspnea or cough. The preoperative electrocardiogram showed digitalis effect but was otherwise normal. A pneumonectomy was performed for a benign granulomatous process which involved the entire right middle lobe and much of the right lower lobe; there was little normal functioning right lung. Pathologic examination showed "multiple organized and ossified areas of infarction or pneumonitis." On the sixth postoperative day, the patient was found to have auricular fibrillation with a rapid, uncontrolled ventricular rate of about 180/minute. His digitalis was increased in an attempt to slow the ventricular rate. The patient fibrillated at a rate of 100 to 120/minute until the tenth postoperative day when he spontaneously reverted to sinus tachycardia. Subsequently, he remained in a normal sinus rhythm until discharge.

CASE 7. M. C., a 70-year-old white man was admitted with dyspnea, cough, hemoptysis and retrosternal "pressure" associated with coughing. Roentgen ray and bronchoscopy suggested a neoplasm. The heart was not remarkable on physical examination. Blood pressure 140/80. A preoperative electrocardiogram was normal. A right pneumonectomy was performed for bronchogenic carcinoma. On the evening of the operative day, the patient developed a right hemiparesis and aphasia, which gradually improved. On the sixth postoperative day, he was found to have auricular fibrillation with a ventricular rate

of 187/minute. The patient was rapidly digitalized with intravenous lanatoside-C which slowed the rate, but he continued to fibrillate with a rate of 110 to 120/minute. He developed progressive respiratory difficulty, sustained auricular fibrillation and expired on the eighth postoperative day. Necropsy revealed mild epicardial fibrosis, a small area of pericarditis, and focal encephalomalacia.

CASE 8. E. S., a 74-year-old white female, had a long history of bronchiectasis. She was admitted with a urinary tract infection and was found to have a suspicious pulmonary shadow on a chest roentgenogram. She complained of dyspnea and cough, but no other

CASE 9. B. M., a 73-year-old white female, was admitted to the hospital with complaints of dysphagia and epigastric pain. The patient was known to have had a hiatus hernia for a number of years. Roentgenography and esophagoscopy were suggestive of an esophageal neoplasm. There were no cardiovascular symptoms. The heart was not enlarged. Blood pressure 170/100. A grade II systolic murmur was heard over the apex and base. The preoperative electrocardiogram showed a nonspecific type of myocardial abnormality with low voltage T waves in the left precordial leads. A subtotal esophagectomy and esophagogastrostomy was performed for an inflam-

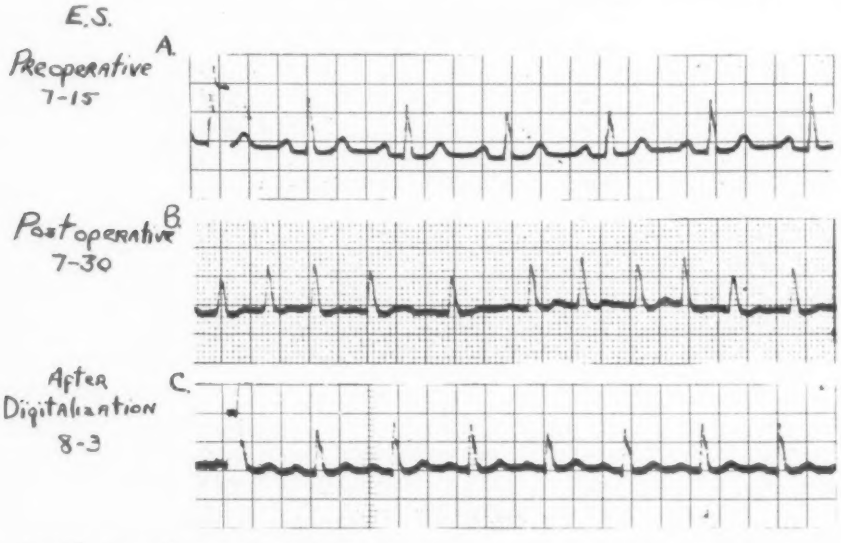

Fig. 2.—Electrocardiograms (Lead II), showing: *A.* Preoperative tracing; normal sinus rhythm with a rate of 90/minute, *B.* Postoperative auricular fibrillation; ventricular rate 165/minute, *C.* Conversion to sinus tachycardia; rate 120/minute.

cardiopulmonary symptoms. On examination, the heart was top normal in size but otherwise negative; the blood pressure was 190/95. The preoperative electrocardiogram was normal. A left pneumonectomy was performed for adenocarcinoma of bronchial origin. The postoperative period was marked by severe dyspnea. On the eleventh postoperative day, the patient was found to have auricular fibrillation, with a ventricular rate of 165/minute. She was rapidly digitalized with intravenous lanatoside-C and within 4 hours the rhythm reverted to a sinus tachycardia at a rate of 120/minute, with rare premature ventricular contractions. She remained in sinus rhythm until discharge (Fig. 2).

ed, stenotic, congenitally short esophagus, with hiatus hernia. No evidence of malignancy was found. On the first postoperative night, the patient developed paroxysmal auricular fibrillation with a ventricular rate of 174/minute. She was rapidly digitalized with lanatoside-C intravenously. The rhythm reverted to a normal sinus mechanism within eight hours, and remained so until discharge.

CASE 10. S. W., a 62-year-old white male, was admitted with the complaint of progressive dysphagia and weight loss. He had a chronic, nonproductive cough and occasionally noted palpitation, but had no other cardiovascular symptoms. Roentgenographic examination revealed a normal heart size with

slight dilatation and tortuosity of the aorta. Examination of the heart was negative. The preoperative electrocardiogram was normal. Roentgenography and esophagoscopy were suggestive of carcinoma of the mid-esophagus. A partial esophagectomy and esophagogastrostomy was performed for squamous cell carcinoma of the mid-esophagus. The afternoon of the first postoperative day the patient developed uncontrolled auricular fibrillation (ventricular rate about 200/minute). He was given a partially digitalizing dose (0.8 mg.) of intravenous lanatoside-C, but approximately 90 minutes later went into acute left ventricular failure with pulmonary edema. Additional lanatoside-C (0.8 mg.) was given (tourniquets, morphine, and oxygen were administered). The ventricular rate gradually slowed, and within 7 hours the rhythm was a normal sinus; the lungs were clear. On the third postoperative night, he again developed auricular fibrillation (ventricular rate 150/minute) and pulmonary edema. He was given additional lanatoside-C intravenously (with tourniquets, and the like) and in about 60 minutes returned to a normal sinus rhythm. On the fourth postoperative night, he had a third episode of rapid auricular fibrillation (ventricular rate 167/minute) and pulmonary edema which promptly responded to treatment, and he remained with a normal sinus rhythm until discharge.

Results. INCIDENCE. Eighty-two patients, of 50 years or older, underwent thoracic surgery during the period under study. The operative procedures included thoracotomy for purposes of exploration, biopsy or resection, exclusive of procedures on the heart, great vessels or pericardium primarily. Ten of these individuals developed a rapid, ectopic rhythm (ventricular rates between 150 to 220/minute), on one or more occasions, in the postoperative period. This represents an incidence of 12.2%.

AGE AND SEX. The study was limited to the older age group, the range of the 82 patients being 50 to 75 years, with a mean age of 60.8 years. The mean age of the 10 patients, who developed arrhythmias, was 66.2 years, with a range of 50 to 74 years. Table 1 is a breakdown by decades, for each group.

Sixty-three males and 19 females comprised the total population. Eight males and 2 females developed arrhythmias.

TABLE 1.—BREAKDOWN BY AGE FOR EACH GROUP

	Total Group		*Arrhythmic Group*	
Age	*Number of Cases*	*%*	*Number of Cases*	*%*
50 to 59	38	46.3	1	1.2
60 to 69	35	42.7	6	7.3
70 to 79	9	11.0	3	3.7
Total	82	100.0	10	12.2

PRE-EXISTING CARDIAC STATUS. Seven of the ten patients observed had clinical evidence of cardiac disease before undergoing surgery (Table 2).

TYPE OF OPERATIVE PROCEDURES. In the entire group, the operations in-

TABLE 2.—CLINICAL EVIDENCE OF CARDIAC DISEASE BEFORE SURGERY

Types of Heart Disease	*Number of Cases*
Arteriosclerotic cardiovascular disease	4*
Hypertensive and arteriosclerotic cardiovascular disease	2
Valvular heart disease (calcific aortic stenosis)	1

*One patient, I. O., had electrocardiographic and historical evidence of an old posterior myocardial infarction. Patient S. S. had a history of three previous episodes of paroxysmal rapid heart action of uncertain type.

cluded intercostal pulmonary biopsy, exploratory thoracotomy, total or subtotal pneumonectomy, and esophageal resection. Table 3 summarizes the operative procedures in the patients who developed arrhythmias.

TABLE 3.—SUMMARY OF OPERATIVE PROCEDURES IN PATIENTS WHO DEVELOPED ARRHYTHMIAS

Operation	*Number of Cases*
Left pneumonectomy	4
Right pneumonectomy	3
Left upper lobectomy	1
Subtotal esophagectomy	2
Total	10

Eight of the operations were for carcinoma. There was one pneumonectomy (J. J. S.) for a chronic, organized pneumonitis with ossification, and one subtotal esophagectomy (B. H.) for esophagitis, hiatus hernia, and esophageal stenosis.

TYPE OF ARRHYTHMIA AND TIME OF ONSET. Patients with premature auricular or ventricular contractions or both, were not included in this study, which was limited to the rapid ectopic rhythms. Table 4 summarizes the data concerning this group.

All of the arrhythmias were verified by electrocardiograms taken at the time of recognition.

Five patients had a solitary postoperative episode of rapid heart action, two of whom died (J. R. and M. C.). Three patients had two bouts of abnormal rhythm, and 2 patients had three separate incidents. Paroxysmal auricular fibrillation was the most frequent mechanism. Eighty-eight per cent of the arrhythmias developed in the first postoperative week. There were no recognized instances of ectopic rhythm during anesthetic induction or during surgery in our group.

TABLE 4.—ONSET AND TYPE OF ARRHYTHMIA

Case	*Onset of Arrhythmia (Postoperative Day)*	*Type of Arrhythmia*
1. I. O.	1	Paroxysmal Auricular Fibrillation
	8	Paroxysmal Auricular Flutter-Fibrillation
2. R. B.	5	Paroxysmal Auricular Flutter
	7	Paroxysmal Auricular Flutter
3. I. B.	2	Paroxysmal Auricular Flutter
	4	Paroxysmal Auricular Fibrillation
4. J. R.	4	Ventricular Tachycardia
5. S. S.	3	Paroxysmal Auricular Fibrillation
	4	Paroxysmal Auricular Fibrillation
	5	Paroxysmal Auricular Fibrillation
6. J. J. S.	6	Paroxysmal Auricular Fibrillation
7. M. C.	6	Paroxysmal Auricular Fibrillation
8. E. S.	11	Paroxysmal Auricular Fibrillation
9. B. M.	1	Paroxysmal Auricular Fibrillation
10. S. W.	1	Paroxysmal Auricular Fibrillation
	3	Paroxysmal Auricular Fibrillation
	4	Paroxysmal Auricular Fibrillation

SUBSEQUENT COURSE. Patient J. R. died during an attack of ventricular tachycardia and pulmonary edema. Necropsy confirmed the clinical impression of calcific aortic stenosis and cardiac enlargement. Case 7 (M. C.) developed a fixed auricular fibrillation and expired with progressive respiratory difficulty. The initial ventricular rate was 187/minute, but this slowed

TABLE 5.—COMPARISON OF AUTHORS' CASES AND THOSE OF OTHERS

Series of Cases	Number of Cases in the Series	Incidence of Arrhythmias		Age		Sex		Pre-existing Heart Disease	Operative Procedures				Arrhythmia		
		Number of Cases	%	Range	Mean	Male	Female	% Pts.	Pneumonectomy		Lobectomy	Esophageal Surgery	Auric. Fib.	Auric. Flutter	Other
									Left	Right					
Graduate Hospital 1952 to 1954	82	10	12.2	50–74	66.2	8	2	70	4	3	1	2	12[2]	3[3]	2[3,4]
Currens, White & Churchill[9]	56[1]	12	21.4	39–65	53	11	1	1	3	3	3	3	8	4[5]	..
Bailey and Betts[2]	141	9	6.4	32–66	48	6	3	0	6	2	1	0	5	2	2[6]
Massie and Valle[22]	78[1]	11	14.1	39–67	52.9	8	3	9	5	6	0	0	5	4	2[6]

1. An additional group of younger patients did not develop an arrhythmia.
2. Five patients had more than one arrhythmia.
3. One flutter-fibrillation; one ventricular tachycardia.
4. One had two bouts of arrhythmia.
5. One had flutter-fibrillation; one nodal tachycardia.
6. Frequent premature contractions; one auricular, one ventricular.

to 90 to 120/minute, with treatment. Postmortem examination demonstrated mild epicardial fibrosis, a small area of pericarditis, and focal encephalomalacia. The two deaths, in the group of 10 patients who developed rapid, ectopic rhythms, represents a mortality of 20%. In both cases the arrhythmia was a primary cause of death.

Patient S. W. developed acute pulmonary edema, due to acute left ventricular failure, in association with each of three periods of auricular fibrillation. He responded to treatment, in each instance, rather promptly. The remainder of the 10 patients seemed to tolerate the arrhythmias well, and, with institution of therapy, reverted to a normal rhythm without evident serious sequelae.

Discussion. Our investigation was limited to those rapid ectopic rhythms appearing in the older age group of patients following thoracic surgery. Table 5 is a comparison of patients in our series with those studied by other authors[2,9,22].

The mean age of our patients is considerably higher than those in the other studies; however, the incidence of ectopic rhythms is not proportionately elevated. In part, this probably attests to advances in anesthesia, improvements in pre- and postoperative care and advances in operative techniques. In contrast to other reports, we found that a significant number of our patients had pre-existing heart disease. The commonest postoperative arrhythmia observed was auricular fibrillation. Most of the operations[2,9,22] were for malignant disease: these included 18 left pneumonectomies and 14 right pneumonectomies. Rapid, irregular heart action in the postoperative period is a dangerous complication, which may result in cardiac failure, myocardial infarction and death[1,2,9,22]; this occurred in two of our cases.

PREDISPOSING AND PRECIPITATING FACTORS IN CARDIAC ARRHYTHMIAS FOLLOWING THORACIC SURGERY. The pathologic physiology of cardiac arrhythmias has been discussed by many authors[5,12,17,19,24,25,26,32]. Those factors which contribute to the development of ectopic rhythms following chest surgery may be arbitrarily considered as predisposing or precipitating factors. In general, the former are inherent in the patient and his disease, while the latter are more closely related to the operative procedure and its effect on intrathoracic physiology and systemic function[1,2,6,7,8,9,22,28,31,33].

Predisposing Factors. These include the age of the patient[9,22,27], the presence of pre-existing heart disease[27], antecedent arrhythmia and frequent premature contractions[20,31]. The nature of the primary lesion is important in that carcinoma of the esophagus or pulmonary malignancy with mediastinal involvement may involve vagal nerve fibers and predispose to arrhythmias[1,8,29]. Ectopic rhythms more frequently follow pneumonectomy than lobectomy[2]. Other factors include certain drugs (premedication)[4,7,14,34], anemia[5,7,22,29] and electrolyte imbalance (CO_2 retention, respiratory acidosis, and others)[5,21,35].

Precipitating Factors. Anoxia, vagal reflexes and hypotension are the major precipitating causes of abnormal rhythms following thoracotomy[2,7,8,10,14,22,29,32,34]. These alterations may be mediated through certain local changes, such as mediastinal shift, atelectasis, empyema, stitch abscess, pleural effusion, pericarditis, irritation of exposed vagal fibers, and tracheal intubation or aspiration. Anesthetic agents, analgesics, muscle relaxant drugs, and even digitalis may contribute to the development of an irregularity of the heart beat postoperatively[4,7,14,34].

The relative importance of any or

all of these factors in a particular case is unique, but it seems certain that, in most cases, several different factors are operative and thereby increase the likelihood of an arrhythmia through a synergistic action.

Treatment. The treatment of abnormal rhythms of the heart beat in older patients following chest surgery is essentially the same as for arrhythmias in other patients of all ages. Therapy is both prophylactic and active. The former is aimed at the correction, elimination or modification of the predisposing and precipitating factors. One cannot, of course, alter the age of the patient, but an alert physician has a therapeutic advantage when postoperative complications arise. Certain measures are imperative, namely, the treatment of pre-existing heart failure, correction of anemia, correction of electrolyte imbalance, prevention of hypoxia and hypotension, and the careful selection of preoperative medication, anesthetic agents, muscle relaxant drugs, and analgesics. The indications, actions, and administration of "antifibrillatory drugs" have been discussed by many investigators[5,16,18,19,24,25,26,29,30,31,33]. The decision as to which agent to use, and when, is an individual problem which must be determined when the need arises. Certain special situations, however, deserve comment. The patient with an antecedent history of spontaneously occurring rapid ectopic rhythms, with or without evidence of heart disease, may benefit by prophylactic antifibrillatory medication prior to extensive thoracic surgery. Preoperative digitalization may prevent the development of supraventricular tachycardia, auricular flutter, and auricular fibrillation[1,15,29,31,33]. Procaine amide or quinidine sulfate may be useful in the patient with frequent premature contractions, particularly if these arise from a ventricular focus[1,18,29,31,33]. Correction of electrolyte imbalance may prevent the development of an ectopic rhythm[1,5]. The judicious use of parasympatholytic agents may diminish the influence of disturbing vagal reflexes[7].

The active treatment of arrhythmias in the post-thoracotomy period demands an aggressive approach, since heart failure and death may supervene. It is mandatory to prevent or correct hypoxia by the use of continuous oxygen inhalations, removal of tracheobronchial secretions, aspiration of pleural fluid, release of tight chest binders, correction of anemia, and the like. The patient should be instructed in deep breathing, which is a helpful adjunct to treatment, before and after chest surgery. Electrolyte disturbances are fairly common in the postoperative period and require prompt correction.

The administration of cardiac medicaments has been discussed at length by others[1,5,15,16,18,19,24,25,26,29,30,31,33]. In our experience, the necessity for parenteral administration of digitalis was answered very well by the use of lanatoside-C preparations. It should be stressed that the patients in our group required rather large doses of digitalis in order to convert the paroxysmal supraventricular arrhythmias and maintain a normal sinus rhythm; however, the dangers of such preparations cannot be overlooked[5,29]. Case 4 (J. R.) who had serious heart disease, and developed left ventricular failure, had premature ventricular contractions before surgery. Digitalis may have contributed to the development of the ventricular tachycardia in this patient, whereas the preoperative administration of procaine amide might have prevented this tragedy.

Summary. Ten of 82 patients of 50 years or older developed rapid ectopic rhythms following thoracic surgery.

The role of predisposing and precipitating factors, in relation to this complication is discussed. Emphasis is placed on the importance of anticipation, early detection, and adequate treatment of these postoperative arrhythmias. The treatment is both prophylactic and active, and must be immediate, vigorous and protracted to be effective.

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THE TREATMENT OF DIASTOLIC HYPERTENSION WITH A FIXED COMBINATION OF HYPOTENSIVE DRUGS

By Jerome M. Waldron, M.D.
ASSISTANT PHYSICIAN TO THE PENNSYLVANIA HOSPITAL

David J. Reinhardt III, M.D.
FELLOW IN MEDICINE

William K. Jenson, M.D.
FELLOW IN MEDICINE

AND

Franz Goldstein, M.D.
FELLOW IN MEDICINE
RESEARCH FELLLOW OF THE AMERICAN HEART ASSOCIATION

(From the Medical Division of the Pennsylvania Hospital [Garfield, G. Duncan, M.D., Director] Philadelphia, Pennsylvania)

In recent years many potent hypotensive drugs have been introduced. Each has proved effective in some patients but none has been found effective in all patients. Undesirable side-effects have been encountered with all of the newer hypotensive drugs in variable proportions of patients. Results in several clinics[2,3,7,8] have shown that combinations of several of the new drugs hold more promise than any one single drug. Combinations apparently affect a greater percentage of patients and produce fewer side-effects because the dosage of each component may be lower than that required when it is used alone[2,7]. Although the pharmacodynamics of these drugs have not been completely elucidated, they appear to act by causing an inhibition of one or more of the following: 1) nerve impulses at the effector organ, 2) ganglionic transmission, 3) pressor reflexes, 4) ill-defined pressor centers, and 5) circulating pressor substances such as angiotonin or pherentasin.

In our Hypertension Clinic we have had experience with all presently used types of hypotensive drugs, used singly and in various combinations. We have found, as have others, that hypertension could be effectively reduced in a larger proportion of patients with combinations of drugs than with any single drug with the exception of the ganglionic blocking agents. Because of the difficulties inherent in their use we have, however, reserved the employment of the latter drugs to emergencies and patients refractory to other drugs. When a combination of *Rauwolfia serpentina*, protoveratrine and phenoxybenzamine (Dibenzyline) in a single capsule became available* we decided to subject this combination to a therapeutic trial. The present report describes the preliminary results of this study.

Materials and Methods. A total of 75 patients were selected for the study but only 38 were followed for a minimum of 6 months' treatment and were fully evaluated. This report concerns these 38 patients. In this group there were 12 males and 26 females; 32 Negroes and 6 whites. All patients selected

*Mio-Pressin, available from Smith, Kline & French Laboratories, Philadelphia, Pa.

for this study had sustained hypertension in excess of 110 mm. of mercury diastolic after a preliminary 2 months' period of placebo medication. Nine patients had control pressures ranging between 160 to 180/110 to 120; 10 patients had pressures between 180 to 200/121 to 130; the remaining 19 patients had initial pressures in excess of 200/130. Only 6 patients of the entire group showed no evidence of cardiovascular damage. Seven patients had suffered cerebrovascular accidents in the past, with or without marked residuals, 13 patients had mild or frank congestive failure and 4 patients had mild nitrogen retention. When classified according to Smithwick's classification, 4 patients were in Group 1, 10 patients in Group 2, 15 in Group 3, and 9 patients were in Group 4. This, then, represents a group of patients with severe hypertension, the majority manifesting evidence of advanced cardiovascular disease.

As indicated before, all patients were placed on lactose placebo for a period of 8 weeks. Patients requiring immediate treatment because of acute complications were excluded from this study. During the period of placebo medication the following studies were obtained: complete blood counts, urinalysis, blood urea nitrogen, PSP excretion, electrocardiogram, teleroentgenogram for heart size, and a funduscopic evaluation by an ophthalmologist. These studies were repeated after 6 months of therapy.

Patients were started on a dose of one capsule 4 times daily, each capsule containing 25 mg. of crude root of *Rauwolfia serpentina*, 0.2 mg. of protoveratrine and 5 mg. of phenoxybenzamine. If a satisfactory response was not obtained after a month the dosage was increased by increments of 4 capsules per day until a maximum of 16 capsules daily was reached. No other measures, such as salt restriction or weight reduction were employed. However, some of the patients attended other clinics where they received therapy for other conditions present. All patients were seen as outpatients in the Hypertension Clinic every 2 weeks. Blood pressures were determined in the sitting and standing positions on each visit. Only the pressures taken in the sitting position are evaluated.

The hypotensive response was graded along the following criteria. The response was considered good (Grade A) if a reduction of pressure by 30/20 from the control average was obtained with the pressures consistently maintained at normotensive levels (below 100 diastolic). The response was considered fair (Grade B) if the drop in pressure was of equal magniturde as for Grade A but with diastolic pressures neither consistently below 100 mm. Hg nor exceeding 110 mm. on more than one visit. Responses of lesser magnitude (Grade C) and no response (Grade D) were grouped together as failures.

Results. Evaluation of changes in blood pressure was based chiefly on the diastolic pressures since the elevation in diastolic pressure is the essence of hypertension. Nineteen of the 38 patients achieved consistently normal diastolic pressures; 9 additional patients had a fair response. Thus a total of 27 of 38 patients showed a satisfactory response (70%). Table 1 summarizes the response of the 38 patients according to Smithwick's classification. All 4 patients in Group 1 had a satisfactory response, with 3 patients maintained at normotensive levels. Eight out of 10 patients in Group 2 had a satisfactory response, with 6 patients showing a return to normotension. The results were equally good in Group 3 where 12 out of 15 patients responded satisfactorily, including 8 patients in whom consistent normotension was maintained. Among the 9 patients in Group 4 only 2 patients returned to normotensive levels, 2 additional patients had a fair response and the remainder were failures. None of the patients with nitrogen retention responded satisfactorily. There were no other features which permitted the prediction of the hypotensive response in the individual patient, although as a group patients with the severest type of hypertension did much worse than did patients in the less severe groups, and patients in Group 1 did uniformly well.

In the patients responding favorably the decline in blood pressure was usually delayed and gradual. In some patients a good response was seen after 2 weeks, but in the majority it took 4 weeks before a significant drop in

blood pressure was apparent and the maximal therapeutic effect was frequently reached only after 6 to 8 weeks. The pulse rate decreased concurrently with the blood pressure. The more rapid reduction in blood pressure observed in some patients would suggest a response to phenoxybenzamine or protoveratrine, or both. The delayed effects are more likely due to Rauwolfia alone, or due to possible synergistic effects of the combination. The two types of responses are depicted in Fig. 1, together with the gradual return toward pretreatment levels when the patients were again placed on placebo.

The decrease in diastolic pressure was not necessarily paralleled by an improvement in the laboratory tests. The changes in these tests after 6 months of treatment are shown in

TABLE 1.—HYPOTENSIVE RESPONSE TO COMBINATION THERAPY IN 38 PATIENTS GROUPED ACCORDING TO SMITHWICK'S CLASSIFICATION

Smithwick Group	*No. of Patients*	*Response Grade**			
		A Number	*B Number*	*C Number*	*D Number*
1	4	3	1	0	0
2	10	6	2	2	0
3	15	8	4	2	1
4	9	2	2	4	1
Totals . . .	38	19	9	8	2

* See text for explanation of response grades.

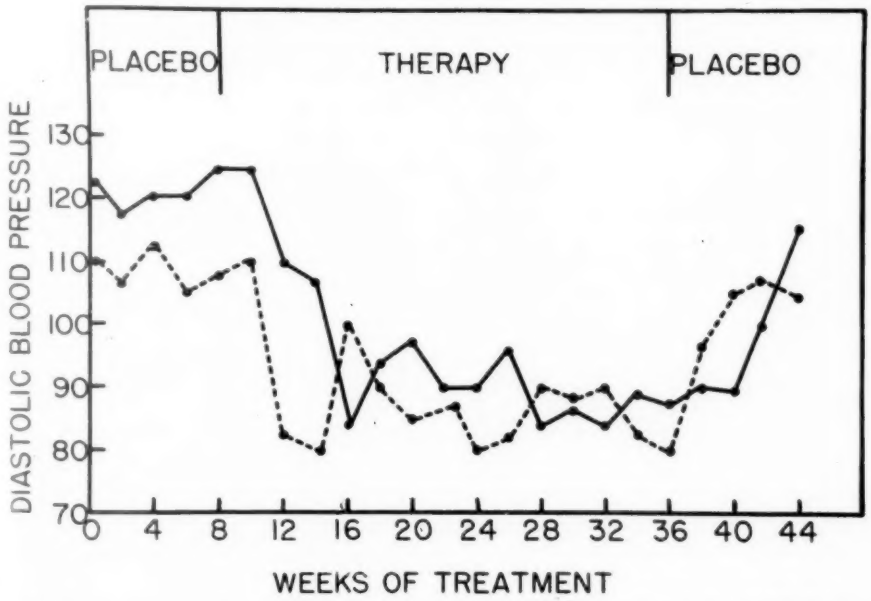

Fig. 1.—Two representative diastolic blood pressure curves during the study. Solid line illustrates the usual slow decrease in pressure. Broken line illustrates the occasional rapid decrease in blood pressure.

Table 2. There was no consistent pattern of improvement except that the greatest number of improvements occurred in the patients who became normotensive. However, in some of the patients in whom normotensive blood pressures were consistently maintained the results of the laboratory tests indicated deterioration. There was no correlation between changes in heart size and in electrocardiographic findings. One might improve while the other became worse. The various laboratory tests were of no help in predicting which patients would respond, with the exception of the blood urea nitrogen (BUN) which, when elevated, in retrospect indicates probable failure of the therapy. There was little change in the eyegrounds in the course of therapy. In 7 patients there was improvement by 1 grade, and in 2 patients there was worsening of the eyegrounds by 1 grade. These changes were usually, but not in all instances, consistent with the type of therapeutic response. The BUN level fell 20 mg. in one patient and rose by 11 to 19 mg. per 100 cc. in 3 patients who were in Smithwick's group 4 from the beginning. The BUN in the remaining patients was not significantly changed in either direction. This is important because it demonstrates that reduction of elevated blood pressure to reasonable levels does not usually affect kidney function adversely.

Table 2.—Changes in Laboratory Tests after 6 Months of Hypotensive Treatment

		Heart Size	*Electrocardiogram*	*PSP Excretion*	*BUN (serum)*
Patients having satisfactory response (Grades A and B)	Improved:	5	9	9	0
	Worse:	4	3	2	2
	*No change:	19	16	17	26
Patients without satisfactory response (Grades C and D)	Improved:	2	1	1	1
	Worse:	0	5	2	2
	*No change:	8	4	7	7

*Changes were not considered as being significant unless they exceeded the following arbitrary limits:
10% in heart size
10% in 20-minute PSP excretion
10 mg. per 100 cc. in serum BUN level

Although side-effects were usually mild, they were noted in 26 out of the 38 patients. The incidence of these side-effects is shown in Table 3. Nasal congestion was a common complaint early in therapy but often disappeared after a few weeks of therapy. Some patients required relief from this congestion by means of nose drops or sprays containing a sympathomimetic agent. Both *Rauwolfia serpentina* and phenoxybenzamine produce nasal congestion, but the incidence of this reaction in this series (39.4%) was no greater than was observed with Rauwolfia alone[2]. The symptom which we list as "fatigue" is more than just tiredness or weakness. It is a positive awareness of fatigue in spite of adequate sleep plus a coexistent lack of "drive." The complaint of lack of "drive" is an important component of the symptom. Fatigue was usually most prominent when the best response to therapy occurred and often disappeared or became less marked after a few weeks. This suggests that the lowering of the blood pressure may have had at least a contributory influence. In 4 male pa-

tients there was complete loss of ejaculatory power during coitus without decrease in the libido. Subsequent experience has shown, however, that this distressing symptom does not occur in nearly as high a proportion of patients as this series would indicate. These 3 symptoms were the major side-effects of therapy. Some patients complained of dizziness and nervousness but these were only exacerbations of continuous symptoms. Nausea was experienced by only 3 patients and in only one was it an isolated symptom. Nausea and the loss of ejaculatory power were observed only in patients receiving large doses. The other side-effects did not appear to be related to the dose.

Table 3.—Incidence of Side Effects

Group	*Nasal Congestion*	*Dizziness*	*Fatigue*	*Nausea*	*Nervousness*	*Loss of Power of Ejaculation*	*Increased Appetite*	*None*
Normotensive	10	3	8	2	1	3	2	8
Fair	2	3	0	1	1	1	1	2
No response	3	2	1	0	0	0	0	2

In the evaluation of new drugs the reasons why patients stop therapy are no less important than the therapeutic response. Thirty-seven of our original group of 75 patients did not complete therapy. Fourteen of these patients were irregular in their clinic visits and were dropped from the study, 5 returned to their private physicians and 11 failed to return to the clinic for reasons unknown. It must be assumed that among the latter group there were patients who did not return because of the side-effects. This possibility is most likely in 3 patients who had previously complained of side-effects. In an additional 3 patients therapy was purposely discontinued because of the occurrence of nausea and vomiting in 1 patient, diarrhea in another and severe prostration in a third patient. The remaining 4 patients were extremely severe hypertensives with uremia who required hospitalization shortly after the beginning of therapy. All 4 patients have died since. In none of them did this combination of drugs succeed in lowering blood pressure.

Concerning the relation of dosage to response the following is noted. Nine of the completely evaluated 38 patients had satisfactory responses with one capsule 4 times daily. Seventeen patients had their doses increased to 2 capsules 4 times daily because of a slow or inadequate response. Of these 17, 13 responded satisfactorily. Ten patients required 3 capsules 4 times a day with 6 satisfactory responses observed. In 2 patients a dose of 4 capsules 4 times a day was tried but no benefit was derived from this dose and the patients who had failed to respond to lower doses also failed to respond to this maximal dose. This experience has been confirmed in additional patients not included in this group.

Comment. The aims of therapy in essential hypertension should be to produce normotension and to halt the progression of pathological vascular changes. In addition to these basic aims, the therapy should produce a minimum of side-effects and the margin between therapeutic and toxic doses should be wide. Any new therapy must be evaluated by these criteria.

Evaluation of the hypotensive effect of new drugs is difficult because of wide variations in the criteria used by various investigators. We feel that the only logical criterion of the efficacy of

a hypotensive regimen is its ability to produce sustained normotension. Evaluation of the response on the basis of only a reduction in blood pressure of any arbitrary magnitude or percentage, but disregarding the level of blood pressure reached, may be very misleading. If the reduction of one patient's pressure from 250/150 to 220/120 is to be hailed as a satisfactory result, the physician may logically wonder whether another patient with an initial pressure of 220/120 should be treated at all. Also, the maintenance of normotension by means of drugs will eventually permit an evaluation of whether the limited present day aim of lowering blood pressure has any ultimate effect on the progress of the vascular disease.

Since neither the etiology of essential hypertension nor the pharmacology of the drugs used to combat it are fully known, the selection of therapy is empirical and is aimed primarily at lowering blood pressure. Studies in many clinics have shown that a combination of two hypotensive drugs is often more effective and produces fewer rather than more side-effects than when any one of the drugs is used alone. The present study deals with a combination of three drugs, each with a different mode of action. Combination therapy will not elucidate the pharmacology of any drug precisely, but if it produces normotension it will aid in the study of hypertensive disease. The therapeutic purist insists on using a single drug, but his position is weak when he uses such galenicals as the crude root of *Rauwolfia serpentina*. It is weaker still when he seeks to make his "single" drug supply the divergent actions required to combat the multiple etiological and supportive mechanisms which are believed to contribute toward the onset and progression of hypertension.

The question arises, of course, whether the number of patients responding to the above combination of three drugs is greater than that responding to any of the drugs used alone or in combinations of two. In our experience with 32 comparable patients treated with Rauwolfia alone, only 12.5% of patients could be maintained at consistently normotensive levels and an additional 12.5% had a fair response. We have had no experience with phenoxybenzamine used alone but reports from other clinics[1,5] indicate that only about 20% or less of treated patients respond favorably. The veratrum drugs used alone usually cause nausea and vomiting in a considerable proportion of patients and, therefore, preclude their successful use in such patients. We have been impressed by the low incidence of nausea and vomiting in patients who are taking combinations of veratrum and Rauwolfia drugs. It may be that Rauwolfia drugs have anti-emetic properties, at least to the extent of antagonizing the emetic properties cof veratrum drugs. This has previously been commented on by Finnerty[2]. Our results also indicate that better results are achieved with the combination of the three drugs, as described here, than with *Rauwolfia serpentina* combined only with protoveratrine. The differences in some patients are striking, but when groups of patients are compared they are only mild. Details of this study will be reported elsewhere.

In the present study the production of normotension in 50% and near-normotension in an additional 20% of 38 patients with mostly severe hypertension is a very favorable response. This was accomplished with relative ease and without severe side-effects. Also, there are definite clinical advantages both in the relatively slow rate of blood pressure lowering while on

therapy and the slow rate of climb when therapy is withdrawn. The disadvantages of a too drastic decline from hypertensive blood pressure levels have been discussed by Grimson, Orgain and their associates[4]. There are reports[6], moreover, of patients who experienced serious or even fatal cerebrovascular accidents following the abrupt withdrawal of potent short-acting hypotensive drugs. The slow rate of blood pressure increase when the combination regimen was stopped would seem to minimize this danger. We have not observed any adverse effects in the immediate period following the interruption of therapy.

The changes in the laboratory tests do not allow definitive evaluation of this therapy. There were changes in either direction with the majority pointing towards improvement. However, the changes were small and may well represent variations within the limits of error of the individual tests in many instances. It will require a considerably longer follow-up and larger numbers of patients before more definite conclusions from the laboratory tests may be reached. Perhaps the most important implication so far is that reducing the blood pressure from hypertensive to normotensive levels does not appear to interfere with the excretory function of the kidneys.

Summary. A fixed combination of *Rauwolfia serpentina*, protoveratrine and phenoxybenzamine was employed in the treatment of 75 patients with hypertension. Thirty-eight of these completed 6 months of treatment and were subjected to a detailed evaluation. Twenty-eight of the 38 patients (70%) had a satisfactory response, with 19 (50%) of them maintained at consistently normotensive blood pressure levels during the course of therapy. The remaining 10 patients responded unsatisfactorily or not at all. The group consisted predominantly of patients with severe hypertension and hypertensive cardiovascular disease. All patients in Smithwick's Group 1 responded satisfactorily. A uniformly poor response was observed in patients with azotemia.

The chief advantages of the described therapy are: 1) ease of administration, 2) minimum of severe side-reactions, 3) large percentage of patients responding satisfactorily even among patients with severe hypertension, and 4) relative safety provided by the delayed reduction in blood pressure after the beginning of treatment and the slow return to control blood pressures following cessation of therapy. The main disadvantages are: 1) high incidence of minor annoying side-reactions, 2) failure of a sizable minority of patients to respond, coupled with the inability in most instances to predict the response in advance.

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PROGRESS
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THERAPEUTICS

UNDER THE CHARGE OF

HARRY GOLD, M.D.

PROFESSOR OF CLINICAL PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE

AND

McKEEN CATTELL, M.D.

PROFESSOR OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, NEW YORK

A REVIEW OF THE TOXICITY OF IRON COMPOUNDS

BY JAMES O. HOPPE, PH.D.
MEMBER

G. MARIE AGNEW MARCELLI, M.S.
RESEARCH ASSOCIATE

AND

MAURICE L. TAINTER, M.D.
DIRECTOR

(From the Sterling-Winthrop Research Institute, Rensselaer, New York)

IN recent years a number of reports have appeared on the poisoning of young children by ferrous sulfate tablets. Iron salts have been freely used as medicaments for thousands of years so that the physician ordinarily is quite unconcerned about any toxic potentialities, particularly when the compound is to be given orally. Since this lack of fear of toxicity seemed inconsistent with the clinical toxicological reports, it became desirable to review the literature on comparative toxicity of various iron salts in experimental animals and in accidental poisonings in patients. The literature survey also indicated the desirability of a new direct experimental comparison under critical conditions of the tolerance of ferrous gluconate and ferrous sulfate. This study has been carried out and is reported elsewhere[38].

History of Iron Therapy. The origin of iron therapy is obscure in the dimness of prehistoric medical experience. It is known to have been employed by the ancient Hindus, Egyptians and Greeks. Iron (apparently as the sulfate) was one of the few inorganic medicines described in the old Egyptian pharmacopoeias. Similarly, in an attempt to bestow the strength of iron upon a patient, Greek physicians administered the metal as a cure for

weakness (which is one of the prominent symptoms of anemia). Water in which red hot iron had been quenched or in which swords had rusted was frequently the medicinal form of iron[30]. Hippocrates also recommended it for both diarrhea and constipation.

In the seventeenth century Sydenham wrote of the treatment of chlorosis by iron[32]:

"To the worn out or languid blood it gives a spur or fillip whereby the animal spirits which before lay prostrate and sunken under their own weight are raised and excited. Clear proof of this is found in the effect of steel in chlorosis. The pulse gains strength, the face (no longer pale and death-like) a fresh ruddy color."

Iron was first shown to be present in the blood in the eighteenth century and Menghini[30] demonstrated that iron in the blood could be increased by feeding foods rich in that substance. Still another significant advance, in the same century, was William Cullen's prophetic warning that the good effects of iron were often missed because of too small doses.

But iron therapy reached its golden age with Pierre Blaud's introduction of his famous pill in 1831[30]. For most of the remainder of the century eulogies proclaiming iron first among all therapeutic agents were common. Then, Bunge, Quincke, and others, finally convinced physicians that inorganic iron was hardly absorbed at all. This, coupled with the unsatisfactory results of injudicious use of iron in all types of anemia, led at last to the "Dark Ages" of iron therapy[21]. Ferrous sulfate, for instance, was not even considered for internal use in the United States Dispensatory of 1918. It was only after the first quarter of the present century that the value of large doses of iron, where iron was needed, was again recognized[29,70].

The frequency of poisoning by iron appears to be a direct function of the fashion in iron therapy in any given period. Opinions on the noxious effects of this substance have varied widely. Sydenham maintained that "iron may be given in the largest doses without inconvenience." However, in 1851, Orfila[54] pleaded, because of the increasing number of accidental and homicidal poisonings from iron salts, for recognition of the toxicity of ferrous sulfate which he and Smith had demonstrated 36 years earlier in *1815*. The law courts of France[7,8,14,44,79] and Italy[28,59] in the middle of the nineteenth century, confused by the divided opinions on the toxicity of iron salts, turned to medical men who carried out animal experiments. Based on these results, iron salts were ruled "poisons" in the legal sense and their administration for felonious purpose constituted "attempted premeditated murder"[59,78].

However, after the turn of the present century, the dispute as to the absorbability of inorganic iron led to the disappearance of iron preparations from the family medicine chest, and iron poisonings vanished. Then observe the trend in thinking on iron as knowledge of the older clinical and experimental reports dimmed and was lost:

1904: "Sufficient evidence exists that ferrous sulfate and ferric chloride have toxic properties"[55].

1928: "Fatal poisoning in man is exceptional"[69].

1934: "Cases of poisoning due to ingestion of iron are extremely rare"[25].

1941: "General intoxication from orally administered iron therapy is unknown"[30].

With the discovery that orally administered iron is utilized in the body and with the gradual acceptance of its safety, particularly when compared to

reactions after parenteral administration[39,43,60], ferrous iron has returned to prominence. In fact so popular is this remedy that five hospitals serving 400,000 people dispensed half a million iron pills in a recent period of 6 months[21].

Since ferrous sulfate tablets are often brightly colored and sugar- or chocolate-coated, they may have a tempting appeal for small children, and hence lead to accidental poisoning[16,22,76]. When reports of such cases began to appear, interest in the toxicology of iron quickened. However, the older literature seems largely to have escaped attention. Thus, Somers[71] reported that "examination of the literature failed to reveal earlier reports of ill effects from orally administered iron compounds. Further . . . we have been unable to find any account of pharmacological investigation into the action of iron given by mouth."

Attention was drawn to this problem in 1952 by the editors of the *Journal of Pediatrics*[19] as follows:

"It is puzzling to understand why medicinal iron preparations, which have been used for generations and which have been looked upon as almost innocuous in overdosage according to medical texts, should first be reported in the last few years as a cause of severe and fatal accidental poisoning in young children. It is obvious that the potential dangers of medicinal iron as a cause of accidental poisoning should be better known to physicians and the public. . . ."

In view of the conflicting evidence and, more important, the increasing frequency of fatalities following the oral ingestion of iron salts, particularly in infants and children, it has become desirable to take a more extensive look at the literature on the toxicity of the iron preparations available for medicinal use. There are summarized below the results of this search of the literature.

Toxicology of Iron Salts in Animals. Estimates of the median lethal dose for several iron preparations by various routes of administration in experimental animals are summarized in Tables 1 to 4. An attempt has been made to express the data in terms of the median lethal dose as mg./kg., both as the salt and its equivalent in terms of ionic iron. The source of the data is indicated in each instance by the reference.

Particularly striking is the fact that relatively few attempts have been made to establish the acute toxicity of these preparations in experimental animals with any degree of precision. In many instances considerable difficulty was encountered by us in attempting, from the published data, to establish the form of the preparation used, the manner in which it was given, duration of the observations, and number of animals employed. Thus, finding a means of expressing the data in standard terminology was a definite problem. From Tables 1 and 4, it becomes possible to arrange the compounds in order of increasing oral toxicity in animals, as follows:

Compound	*Species*	*Estimated Oral LD_{50} mg./kg.*
Ferrous gluconate	mouse	6600
	guinea pig	2100
	rabbit	3500
Ferric ammonium citrate	mouse	5000
	guinea pig	1750
	rabbit	2800
Ferrous sulfate ($FeSO_4 \cdot 7H_2O$)	mouse	4500
	guinea pig	1500
	rabbit	3000
	cat	>500
	dog	800
Ferric chloride	mouse	1500
	guinea pig	600
	rabbit	1200
Ferrous chloride	rat	600
	rabbit	1000

TABLE 1.—TOXICITY OF FERROUS SULFATE (ORAL ADMINISTRATION)

	Dose*		LD_{50} mg./kg.			
Species	*As Salt*	*As Fe^{++}*	*As Salt*	*As Fe^{++}*	*Comments*	*Ref.*
Mouse	..	..	4500	900	$FeSO_4$ crystalline	71
	..	..	4100	1000	$FeSO_4$ as "Fersolate"	71
	..	..	..	710		13
Frog	..	29.4 mg.	..	..	Fatal. Animal wts. 35 to 45 gm.	73
Rat	..	73.6 mg.	..	..	1/3 died. Animal wts. 100 to 200 gm.	73
Guinea pig	400 mg.	..	..	..	Fatal 18½ hrs. Fe as "Fersolate"	25
	200 mg.	..	..	..	Fatal in ½ hr.	25
	400 mg.	..	..	..	Survived } Fatal dose equals	25
	600 mg.	..	..	..	Fatal } 65 mg./64 gm.	25
	800 mg.	..	..	..	Fatal	25
	..	..	1500	300	$FeSO_4$ crystalline	71
	..	..	1250	300	$FeSO_4$ as "Fersolate"	71
Rabbit	..	..	3000	600	$FeSO_4$ crystalline	71
	..	..	3000	720	$FeSO_4$ "Fersolate"	71
	3000 mg./kg.	..	..	..	With 3 gm. $NaHCO_3$. Survived	71
	3000 mg.	..	..	..	Fatal	79
	..	368 mg./kg.	..	..	Ill but survived	73
	..	736 mg./kg.	..	..	Fatal	73
	1000 mg.	..	..	..	In 30 to 50 gm. corn meal. No ill effects	28
	4327 mg./kg.	..	..	..	Fatal 3 to 4 hours	28
	1869 mg./kg.	..	..	..	Fatal < 1 hour	28
	769 mg./kg.	..	..	..	Fatal 1½ hours	28
	540 mg./kg.	..	..	..	Ill but survived	28
Cat	1000 mg.	240 mg.	..	..	5 "Fersolate" tablets. Survived	25
Dog	2000 mg.	..	..	..	Ill but survived	69
	8000 mg.	..	..	..	Fatal in 26 hrs.	54
	930 mg./kg.	..	..	..	Fed in cornmeal. Ill but survived	28

* Where the dose is given only as the salt, the authors have not indicated the state of hydration and, therefore, the absolute iron content cannot be calculated.

TABLE 2.—TOXICITY OF FERROUS SULFATE (INTRAVENOUS ADMINISTRATION)

	Dose*		LD_{50} mg./kg.			
Species	*As Salt*	*As Fe^{++}*	*As Salt*	*As Fe^{++}*	*Comments*	*Ref.*
Mouse	..	..	..	13.8		13
	..	..	..	11		51
Rabbit	..	30–60 mg./kg.	..	..	Fatal dose lies in this range	47
	..	10–15 mg./kg.	..	..	Fatal in nine hours	69
Cat	..	30–60 mg./kg.	..	..	Fatal dose lies in this range	47
Dog	..	30 mg./kg.	..	..	Lethal dose for dog	47
	400–500 mg.	..	..	..	Ill but survived	54
	..	10 mg./kg.	..	..	No effect	74
	..	20 mg./kg.	..	..	Fatal in three hours	74
	..	70 mg./kg.	..	..	Immediate death	74

* Where the dose is given only as the salt, the authors have not indicated the state of hydration and, therefore, the absolute iron content cannot be calculated.

TABLE 3.—TOXICITY OF FERROUS SULFATE (RECTAL AND TOPICAL ADMINISTRATION)

		Dose*				
Species	*Route of Adminis.*	*As Salt*	*As Fe^{++}*	*Tissue Irritation*	*Comments*	*Ref.*
Rat	Rectal	..	36.8 mg.	..	Fatal in 3 hrs. }	73
		..	73.6 mg.	..	Died in ½ hr. } Wt. 100 to 200 gm.	73
		..	73.6 mg.	..	Died in 4 hrs. }	73
Rabbit	Rectal	..	368 mg./kg.	..	Fatal in 6 hours	73
Dog	Topical	8000 mg.	..	Intense	Fatal in 12 to 27 hours when applied to cellular tissue of thigh	54

* Where the dose is given only as the salt, the authors have not indicated the state of hydration and, therefore, the absolute iron content cannot be calculated.

TABLE 4.—TOXICITY OF OTHER IRON SALTS

Salt	*Species*	*Route of Admin.*	*Dose**		*LD_{50} mg./kg.*		*Comments*	*Ref.*
			As Salt	*As Fe^{++}*	*As Salt*	*As Fe^{++}*		
Ferrous glucon.	Mouse	Oral	..	..	6600	1100	Figures are those reported by the author who indicated iron content as 16 2/3%	71
	Guinea pig	"	..	..	2100	350		71
	Rabbit	"	..	..	3500	580		71
Ferrous chlor.	Frog	"	..	22 mg.	..	..	Fatal in 24 hrs. Wt. 35 to 45 gm.	73
	"	"	..	33 mg.	..	..	Fatal in 4 hrs.	73
	Rat	"	..	14 mg.	..	..	Somewhat ill (Wt. 100 to 200 gm.)	73
	"	"	..	18 mg.	..	..	Somewhat ill (Wt. 100 to 200 gm.)	73
	"	"	..	28 mg.	..	..	1/2 died after 24 hrs. (Wt. 100 to 200 gm.)	73
	"	"	..	56 mg.	..	..	Fatal 7/7 in ½ to 30 hrs. (Wt. 100 to 200 gm.)	73
	Rabbit	"	..	168 mg./kg.	..	..	No effect	73
	"	"	..	224 mg./kg.	..	..	2/2 no effect	73
	"	"	..	252 mg./kg.	..	..	Fatal in 24 hrs.	73
	"	"	..	280 mg./kg.	..	..	Fatal in 5/5 in 24 to 48 hrs. Higher doses all fatal	73
Ferrous carb.	Mouse	"	..	..	31000	3800	As Blaud's Pills	71
	Guinea pig	"	..	..	16000	2000	" " "	71
	Rabbit	"	..	..	17800	2220	" " "	71
Ferric chlor.	Mouse	"	..	..	1500	500		71
	"	"	..	..	..	840		13
	Guinea pig	"	..	..	600	200		71
	Rabbit	"	..	..	1200	400		71
	Dog	"	3.75–5 gm.	..	..	..	Fatal in 27 to 30 hrs.	59
	"	"	2.5 gm.	..	..	..	Severely ill one week, impaired digestive process	59
Ferric ammon. cit.	Mouse	"	..	..	5000	1000		71
	Guinea pig	"	..	..	1750	350		71
	Rabbit	"	..	..	2800	560		71
Sodium ferricit.	Rat	"	..	37.2 mg./kg.	..	..	1/2 dead in 2 hrs.	73
	Rabbit	"	..	186 mg./kg.	..	..	Fatal in 4 hrs	73
Ferrous chlor.	Dog	I.V.	..	10 mg./kg.	..	..	No effect	74
	"	I.V.	..	30 mg./kg.	..	..	Fatal in 8 hrs.	74
Ferric chlor.	Mouse	I.V.	..	..	..	18.5		13
Ferric ammon. cit.	Mouse	I.V.	..	..	..	16.5		51
Sodium ferricit.	Frog	S.C.	..	5–10 mg.	..	..	Produced paralysis	48
	Rabbit	I.V.	..	25 mg./kg.	..	..	Average lethal dose	48
	Cat	I.V.	..	30-60 mg./kg.	..	..	Lethal. No symptoms for 3 days	48
	Dog	I.V.	..	20-50 mg./kg.	..	..	Lethal	48
Ferrous bicarb.	Dog	I.V.	..	5 mg./kg.	..	..	No effect	74
	"	I.V.	..	10 mg./kg.	..	..	Fatal in 3 hrs.	74
Ferric tartrate	Mouse	I.V.	..	..	..	16.5		51
Ferrous chlor.	Rat	Rectal	..	28 mg.	..	..	Fatal in 48 hrs.	73
	"	"	..	56 mg.	..	..	Fatal in 5 min.	73
	Rabbit	"	..	280 mg./kg.	..	..	Fatal in 1/2 in 5 hours	73
Sodium ferricit.	Rat	"	..	37 mg./kg.	..	..	Fatal in 5 hrs.	73
	Rabbit	"	..	186 mg./kg.	..	..	Fatal in 4 hrs.	73

* Where dose is given only as the salt the authors have not indicated the state of hydration and, therefore, the absolute iron content cannot be calculated.

I.V. = intravenous S.C. = subcutaneous

The intravenous toxicity data are a little more difficult to appraise due largely to the paucity of data. The available data indicate one fact with striking clarity: these preparations are considerably more toxic by the intravenous than by the oral route of administration. The intravenous toxicity of ferrous sulfate in mice appears to be approximately 70 mg./kg.[13]. Interestingly, the intravenous toxicity value for ferric chloride appears to be of an order of magnitude similar to that for ferrous sulfate. An intravenous value of 30 mg./kg. of iron or approximately 107 mg./kg. of salt was reported for ferrous chloride in the dog[73].

Following oral administration of toxic doses of ferrous sulfate and related compounds in the mouse and rat, the animal becomes depressed within a few minutes. This depression deepens into complete prostration during which the respiration becomes shallow and rapid. Most of the deaths usually occur within 2 to 6 hours, following a brief terminal convulsive episode. Cessation of respiration precedes cardiac arrest. Those animals which survive invariably show evidence of an intense diarrhea the day following medication. These survivors also exhibit a decreased interest in food for a day or so and frequently there are delayed deaths during the first 2 or 3 days. Toxic symptoms in higher species, such as the cat and dog, appear to be similar except that copious vomiting is produced in contrast to the lower rodent species, where this protective mechanism is absent.

Inspection of the viscera immediately following death reveals the presence of mild to severe congestion of the gastric mucosa even to the point of fresh blood in the stomach, depending upon the dose and concentration of the preparation administered. Hyperemic to petechial hemorrhagic areas may be found in the small intestine. The liver usually shows marked congestion and several to many petechial hemorrhagic areas are usually seen in the lungs. Tissue changes present at death occurring several days after oral medication include marked erosion of the gastric mucosa with fibrotic changes particularly in the greater curvature and antrum, and congestion in the liver, lungs and kidney.

Recently, Nissim[52] called attention to the capillary damaging and anticoagulant effects of various iron preparations and the striking agreement with the incidence of extensive hemorrhages in the lungs with these preparations. Interestingly enough, some 90 years ago, Tourdes[79] observed a "thinning of the blood" in experimental animals suffering from iron intoxication and had suggested that ferrous sulfate may inhibit the coagulation of blood.

CHRONIC TOXICITY OF IRON COMPOUNDS. Studies by Hendrysch and Klimesch[35], using ferrous carbonate, ferrous chloride, and sodium ferricitrate intramuscularly or subcutaneously in rabbits and dogs, showed that administration of small amounts of these iron compounds over periods up to 4 months produces a chronic and sometimes fatal poisoning. These authors concluded that the differential toxicity of iron salts is not based strictly on iron content. Hoff[36] administered small daily doses of ferric chloride (about 300 mg. of iron or about 870 mg. of anhydrous ferric chloride) to a dog in which the liver was by-passed by means of an Eck fistula. "Chronic cerebral intoxication" was reported.

Clinical Toxicity. Ferrous sulfate is the causative agent in the majority of iron poisonings, but fatal ingestion of ferrous chloride, ferric chloride, and ferric ammonium citrate has been reported. In every case, nineteenth century and contemporary, the clinical

aspects have been surprisingly similar. Initially there appear nausea and some vomiting, progressing to severe gastroenteritis with hematemesis, abdominal pain, and diarrhea. Lassitude is followed closely by development of marked shock, usually 4 to 6 hours after ingestion. If the patient survives this collapse, there generally ensues a period of considerable clinical improvement. A second crisis occurs 20 to 50 hours after ingestion of the iron preparation; and if this latter stage of shock, arising from gastric mucosal corrosion, does not terminate fatally, recovery is usually ensured. Hematochezia, convulsions, and motor disturbances are seen occasionally[1,19,31,64,75,79]. Postmortem findings include necrosis of the gastric and intestinal mucosa and congestion or necrosis of the liver. In addition, lung and kidney congestion are frequently observed. Fatal outcome following overdosage with iron varies widely, not only with dose, but also with age, physical condition, and individual susceptibility.

CASE REPORTS ON OVERDOSAGE WITH ORALLY INGESTED IRON PREPARATIONS

A. *Ferrous Sulfate (36.76% iron in anhydrous salt, 20.09% in USP crystalline).* Ferrous sulfate has been the toxic agent in nearly all the reported poisonings, accidental and homicidal. Of the 63 cases with this salt, 23 (two adults and 21 children) ended fatally. In many of the recent instances, the source of iron was "Fersolate," a British proprietary preparation consisting of 200 mg. (3 gr.) of $FeSO_4$, 2.6 mg. (1/25 gr.) of $CuSO_4$, and 2.6 mg. (1/25 gr.) $MnSO_4$ per sugar coated tablet. As few as 15 to 16 of these tablets in a single dose have proved fatal to a 19-month-old child, and 8 are reported to have produced a severe reaction in a child of 2 years. It should be noted that laboratory tests indicate that neither the manganese nor the copper sulfate present contribute materially to the toxic action[25,71]. Obstruction of the stomach occurred in 7 cases. Two instances are considered in detail, one a 3-year-old boy who had ingested about 67 ferrous sulfate tablets[10] and the second, a 17-month-old boy who swallowed 6 to 12 "Fersolate" tablets[62]. Each patient exhibited typical symptoms of ferrous sulfate poisoning so that gastric lavage was performed and anti-shock treatment administered. After several days, both had improved and were vomiting only occasionally. About 3½ weeks after ingestion, emesis increased in frequency and severity. Radiograms made 4 hours after a barium meal showed no barium had left the stomach of either child. In the first case, the stomach was empty 24 hours later, but in the second, only a small amount of barium was observed in the transverse colon after approximately 20 hours. Both children were clinically worse and surgery seemed the best course. Upon operation, thickening and stenosis of the pylorus were found, which were more severe in the case of the younger child. The first patient made a satisfactory recovery, but the second died of acute suppurative peritonitis following the operation.

In both animals and humans who have died after overdoses of iron, hemorrhagic gastritis with edema has been observed in postmortem examination. Both Crosskey and Ross felt that fibrous contracture of the pyloric antrum and pyloric stenosis probably resulted from this persistent intense gastritis.

A summary of fatal cases appears in Table 5 and of nonfatal, in Table 6.

It should be pointed out that in many cases authors have not identified the preparation nor indicated the state of hydration of the ferrous sulfate. Different manufacturers declare in terms of the anhydrous, exsiccated or

U.S.P. (crystalline) salt; some make no indication at all of the state of hydration. Generally, one can assume that the 0.2 gm. tablets are exsiccated ferrous sulfate U.S.P. (approximately 30% iron) and the 0.3 gm. ones are U.S.P. crystalline ferrous sulfate (approximately 20% iron), although this is not invariably the case. Further confusion exists among different official prepara-

TABLE 5.—SUMMARY OF DEATHS DUE TO FERROUS SULFATE

No.	*Year*	*Age*	*Sex*	*Approximate Dose of $FeSO_4$**	*Time of Death after Ingestion*	*Comments*	*Ref.*
1	1850	Child	?	? plus alum	?	Murder. Sentenced to 10 years enforced labor	14
2	1851	Adult	M	? in beef broth	36 hrs.	Murder. Wife condemned to death	8
3	1851	4 yrs.	?	?	?	Murder	54
4	1851	10 mo.	F	50 gm.	36 hrs.	Murder	54, 78
5	1888	5 yrs.	M	648 mg.	24 hrs.	Accident. Intended as an anthelmintic	24
6	1947	3½ yrs.	M	10 gm.	53 hrs.	Accidentally ingested 50 Fersolate tablets	25
7	1947	16 mo.	F	5.2 gm.	21 hrs.	Accident. Source was 26 Ferosolate tablets	76
8	1947	12 mo.	M	6–7 gm.	30 hrs.	Accident. 30 to 35 Fersolate tablets. Treated for shock and aspiration pneumonia	25
9	1948	26 yrs.	M	115 gm.	3 hrs.	About ¼ lb. of U.S.P. ferrous sulphate	27
10	1949	11 mo.	F	?	39 hrs.	Accidentally ingested unknown quantity of Fersolate tablets	57
11	1950	17 mo.	F	6 gm.	11 hrs.	Accident. No more than 20 × 0.3 gm. $FeSO_4$ tablets. Methylene blue gave temporary improvement.	67
12	1951	12 mo.	M	?	4½ hrs.	Accident. Unknown number of $FeSO_4$ tablets. Only medical treatment consisted of castor oil	72
13	1951	19 mo.	F	3.0–3.2 gm.	4¾ hrs.	Accident. 15 to 16 $FeSO_4$ tablets. Two hospitals refused admission. Doctor prescribed orange juice	72
14	1951	18 mo.	M	8.8 gm.	5½ hrs.	Accident. 44 $FeSO_4$ tablets. Stomach lavaged. Restoratives given	72
15	1951	14 mo.	F	8 gm.	20 to 24 hrs.	Accident. 44 $FeSO_4$ tablets. Returned 4. Doctor felt no danger, prescribed castor oil and kaolin	72
16	1952	26 mo.	F	9 to 12 gm.	4½ hrs.	Accident. 30 to 40 × 0.3 gm. chocolate coated tablets. Gastric lavage plus supportive therapy	12
17	1952	19 mo.	M	?	40 hrs.	Accident. Unknown number enteric coated 0.2 gm. tablets. Gastric lavage, supportive therapy, antibiotics, BAL without improvement	75
18	1952	21 mo.	M	8.2 gm.	4 hrs.	Accident. About 41 Fersolate tablets. Gastric lavage with sodium bicarbonate	66
19	1952	17 mo.	M	?	?	Accident. Unknown quantity of tablets	80
20	1952	2 yrs.	M	13.8 gm.	7 hrs.	Accident. About 43 × 0.32 gm. $FeSO_4$ tablets	80
21	1953	29 mo.	M	22.5 gm.	4½ hrs.	Accident. 75 × 0.3 gm. tablets. Gastric lavage	4
22	1954	20 mo.	F	10.2 to 14.2 gm.	20¾ hrs.	Accident. 34 to 44 × 0.3 gm. enteric coated $FeSO_4$. Supportive therapy	9
23	1954	21 mo.	F	?	48 hrs.	Accident. ? × $FeSO_4$ exsic. 0.162 gm. + liver conc. NF. Supportive therapy	11

NOTE: Cases 1 to 5 were probably $FeSO_4 \cdot 7H_2O$ but authors do not so indicate. Cases 12 to 15 were probably Fersolate.

* Based on each author's report. No attempt has been made to convert U.S.P. crystalline ferrous sulfate ($FeSO_4 \cdot 7H_2O$). [See text.]

TABLE 6.—NONFATAL POISONING FROM FERROUS SULFATE

No.	*Year*	*Age*	*Sex*	*Approximate Dose of $FeSO_4$**	*Length of Convalescence*	*Comments*	*Ref.*
1	1850	22 yrs.	F	?	?	Attempted murder. Husband sentenced to 5 yrs. Nearly fatal. Commercial green vitriol	7
2	1859	36 yrs.	M	? gm. in wine	3 days	Attempted murder. Commercial ferrous sulfate. Seriously ill	78
3	1881	17 yrs.	M	?	..	Attempted murder. Commercial ferrous sulfate. Small amount of cornmeal. Slightly ill.	28
4	1881	12 yrs.	F	?	Several days	Sister of Case 3. Poisoned on same occasion	28
5	1881	45 yrs.	F	?	2 weeks	Mother of Cases 3 and 4. Poisoned on same occasion	28
6	1881	70 yrs.	M	?	2 days	Father of Cases 3 and 4. Poisoned on same occasion	28
7	1883	40 yrs.	F	56 gm.	3 mo.	Attempted suicide. Stormy course for more than 2 mos.	34
8	1934	Child	F	28 gm.	?	No details given	25, 67, 68
9	1936	30 yrs.	M	32.4 gm. in 26 days	?	3 × 0.375 gm. per day. Anemia therapy. Epileptiform seizures. Patient weighed 86.5 lbs.	50
10	1936	Adult	F	24.75 gm. in 33 days	?	0.75 gm./day. Anemia therapy. Epileptiform seizures	50
11	1947	2 yrs.	M	1.6 gm.	15 days	Accident. 10 Fersolate tablets. Returned 2. Emetics and supportive therapy	76
12	1949	16 mo.	M	6 gm.	1 week	Accident. About 50 Fersolate tablets. Returned 20. Gastric lavage, supportive therapy and BAL	63
13	1950	4½ yrs.	F	0.8 gm.	..	Accident. 24 Fersolate tablets. Returned 20. Received 0.15 gm. $NaHCO_3$ every 4 hrs.	77
14	1950	19 mo.	M	2 gm.	..	Accident. About 10 Fersolate tablets. Gastric lavage with $NaHCO_3$; BAL	77
15	1950	2½ yrs.	M	2 to 4 gm.	..	Accident. 10 to 20 Fersolate tablets. Given syrup of figs	77
16	1951	14 mo.	?	4 gm.	..	Accident. 19 to 20 $FeSO_4$ tablets	6
17	1951	2½ yrs.	F	?	3 days	Accident. About 60 $FeSO_4$ tablets but returned "nearly all"	72
18	1951	21 mo.	F	10.8 gm.	26 days	Accident. About 75 $FeSO_4$ tablets but returned 21. Gastric lavage	72
19	1951	23 mo.	M	6.5 gm.	3 weeks	Accident. 16 $FeSO_4$ tablets and 10 iron "plastules." Returned 4 tablets and partly dissolved "plastules"	72
20	1951	11 mo.	M	1.4 to 1.8 gm.	3 days	Accident. 13 $FeSO_4$ tablets but returned pieces = to 4 to 6 tablets. Gastric lavage	72
21	1951	20 mo.	M	0.6 gm.	3 hrs.	Accident. About 5 $FeSO_4$ tablets but returned 2. Ill enough to hospitalize	72
22	1951	30 mo.	F	15 gm.	11 days	Accident. Believe about 75 × 0.2 gm. $FeSO_4$ tablets. Gastric lavage. $NaHCO_3$. Penicillin	49
23	1952	15 mo.	F	4.5 to 6 gm.	54 hrs.	Accident. 15 to 20 × 0.3 gm. $FeSO_4$ tablets. Tablet fragments returned	12
24	1952	18 mo.	M	4.5 gm.	7 days	Accident. 15 × 0.3 gm. $FeSO_4$ tablets. Gastric lavage, plasma, penicillin	12
25	1952	3 yrs.	M	?	2½ mo.	Accident. 67 × ? gm. $FeSO_4$. Gastric lavage, nikethamide, and methionine. Pyloric stenosis necessitated surgery	10
26	1952	19 mo.	F	?	1 week	Accident. 10 × ? $FeSO_4$ tablets. Gastric lavage and supportive therapy	40

TABLE 6.—NONFATAL POISONING FROM FERROUS SULFATE—(*Continued*)

No.	*Year*	*Age*	*Sex*	*Approximate Dose of $FeSO_4$**	*Length of Convalescence*	*Comments*	*Ref.*
27	1953	17 mo.	M	1.2 to 2.4 gm.	Died of peritonitis following surgery	Accident. 6 to 12 Fersolate tablets. Gastric lavage and antishock treatment. Pyloric stenosis necessitated surgery twice	62
28	1954	14 mo.	F	15 to 22.5 gm.	10 days	Accident. 50 to 75 × 5 gr. $FeSO_4$ tablets. Gastric lavage and BAL	65
29	1954	21 mo.	F	?	8 weeks	Accident. Unknown number of Fersolate. Pyloric stenosis requiring surgery	81
30	1954	2 yrs.	M	8 gm.	1 mo.	Accident. 40 Fersolate. $NaHCO_3$ lavage returned broken tablets. Pyloric stenosis treated surgically	81
31	1954	26 mo.	F	13 gm.	6 days	Accident, 65 capsules × 0.2 gm. $FeSO_4$, 3.25 mg. molybdenum oxide. Gastric lavage. I.V. $NaHCO_3$ and BAL	3
32	1954	16 mo.	F	?	8 weeks	Accident. ? × Ferrous Sulfate tablets. Vomited 20. $NaHCO_3$ lavage. Pyloric stenosis required surgery	23
33	1954	15 mo.	F	2.4 gm.	4 days	Accident. 8 × 0.3 gm. $FeSO_4$ tablets, enteric-coated	9
34	1954	13 mo.	F	3.8 to 5.7 gm.	8 days	Accident. 20 to 30 × 0.19 gm. $FeSO_4$ tablets. $NaHCO_3$ lavage. Supportive therapy	42
35	1954	17 mo.	F	2 to 3 gm.	3½ mo.	Accident. 10 to 15 Fersolate. Supportive therapy. Pyloric obstruction required surgery	26
36	1954	13 mo.	M	?	2 mo.	Accident. ? × Fersolate. $NaHCO_3$ lavage. Supportive therapy. Pyloric obstruction treated surgically	26

NOTE: No details available on 4 other nonfatal cases.[66] Cases 17 to 21 are probably Fersolate.

* Based on each author's report. No attempt has been made to convert to U.S.P. crystalline Ferrous Sulfate ($FeSO_4 \cdot 7H_2O$). [See text.]

tions of the exsiccated form, the U.S.P. material containing not less than 80% anhydrous salt, $FeSO_4$ exsic. B.P. not less than 77%, and official material in Norway 80.5 to 85%. "Fersolate," for instance, declares 0.2 gm. exsic. $FeSO_4$ (at least 77% anhydrous salt equivalent to about 29% ferrous iron); but a publication from the manufacturer's research laboratories reports the iron content as 24%[71]. Thus, actual dose in terms of anhydrous or U.S.P. crystalline ferrous sulfate or ferrous iron content frequently cannot be determined with any accuracy.

In some instances (Table 5, Nos. 12, 13, 15), the children remained at home with little or no medical care beyond castor oil and reassurance. Lack of appreciation of the reality of ferrous sulfate poisoning by doctors and hospitals makes it necessary to emphasize that ferrous sulfate intoxication may be serious, and that immediate treatment is essential[12,17].

B. *Ferrous Chloride (44.06% iron in anhydrous salt, 28.09% in crystalline tetrahydrate)*. The use of ferrous chloride in Sweden has resulted in at least 3 cases of iron toxicity. A 2½-year-old girl swallowed about 20 tablets, each containing 0.267 gm. of ferrous chloride (5.34 gm.). The child exhibited typical symptoms of iron poisoning, but

survived. Some residual signs of stomach damage were still evident by roentgenogram 6½ months after ingestion of the tablets and the child's general condition continued poor for a considerable time[45]. In the same report, Lindquist noted a second case of very severe ferrous chloride poisoning following ingestion of about 40 tablets of 0.267 gm. of $FeCl_2$. Extensive necrosis through all the layers of the stomach wall was observed.

More recently a third case, that of a 17-month-old boy, has been reported[56]. The child, while playing with its mother's anti-anemia iron tablets, swallowed an unknown number. No symptoms developed till 4 hours later, and within one-half hour his condition was serious enough to require hospitalizaation. Methylene blue plus intravenous fluids brought about a decided improvement, but the child's condition once more began to deteriorate so that, in spite of continued therapy, he expired 28 hours after ingestion of the tablets.

Lindquist suggests that the assertion in a pharmacology text that ferrous chloride had no caustic effect and that overdosage involved no risk, was probably based on the paucity of reported cases from ferrous chloride. However, on the basis of the cases reported, he concluded that ferrous chloride, like ferrous sulfate, may prove very dangerous, at least to children.

C. *Ferrous Gluconate* (*12.52% iron in anhydrous salt, 11.58% in dihydrate*). Ferrous gluconate, since the work of Reznikoff and Goebel[60,61] reported in 1937, has become increasingly popular as a source of iron in anemia therapy. It is the most readily absorbed of all ferrous salts[33] and has been found to produce less gastric upset[33,60,61]. Holly[37] recently reported on the administration of ferrous gluconate to pregnant, nonpregnant, anemic and normal females. Patients received as much as 1 gm. per day for up to 76 days without indication of ill effects.

Toxic symptoms are apparently exceedingly rare beyond occasional nausea, and the like, in susceptible individuals, and even here symptoms are less severe than with other forms of iron[37,60]. No reports have been found in the literature of poisoning from this salt, and the medical files of a major producer of this preparation contain no privately reported cases of reactions following overdosages in humans[82]. Further, an English source has indicated recently that 8 ferrous gluconate (Fergon) tablets were ingested, without any untoward effects, by an 11-month-old girl[2]. Clinically, at least, this iron salt appears less irritating and less toxic than other common sources of iron.

D. *Ferric Ammonium Citrate* (*14.5 to 16% iron in the green salt, 16.5 to 18% in the brown form*). Ferric ammonium citrate has become a common medicinal form of iron, since it has been found to be utilized by the body and is lacking in the objectionable astringent properties found in simple ferric salts[5]. However, this salt is not without toxic effects.

In 1949, a 26-year-old pregnant woman took a mixture of 15 gm. of iron ammonium citrate in whiskey, apparently in the hope of inducing an abortion. She died 3 days later of toxic hepatitis[15]. Hurst[41], in 1931, reported a case of iron encephalopathy resulting from iron ammonium citrate. A 58-year-old woman, suffering from anemia, while in the hospital, received 4 × 40 gr. (10 gm.) of the iron salt per day for 23 days. On the 24th day, the daily dose was increased to 2 × 40 gr. plus 2 × 60 gr. (12.5 gm.). Nine times the following morning the patient, while vomiting, lost consciousness. Her breathing became stertorous, the face

was cyanosed, eyes deviated to the right, and pupils dilated. Plantar reflexes were extensor. Between attacks, the patient was semi-conscious and appeared to have a headache. Iron therapy was stopped and the patient gradually recovered.

E. *Ferric Chloride (34.43% iron in anhydrous salt, 20.66% in hexahydrate).* Ferric chloride was the toxic agent employed in 4 homicides reported by Peterson *et al.*[55]. As little as 1½ oz. (45 cc.) of tincture of ferric chloride (6 gm. of salt) proved fatal to an adult male when taken internally. However, in 4 cases involving 1 to 3 oz. of this tincture, the women survived in each case[68]. Ravaglia, in 1884[59], recorded a case of attempted murder with ferric chloride. The woman survived but was troubled by a general dyspeptic disturbance for one month.

Human Lethal Dose. Any attempt to estimate the human fatal dose of these preparations must be made in full recognition of the inherent errors involved. The data are collected from accidental poisoning cases in which it is often difficult or impossible to establish with accuracy the amount consumed. Even though the error may be large, it becomes of interest to examine the summary of the case reports of deaths due to ferrous sulfate as given in Table 5. In several instances reasonably accurate information was available on the amounts of ferrous sulfate ingested. It is possible to make a rough approximation of the fatal dose in terms of mg./kg. of ferrous sulfate for some of the cases.

Death has occurred from the oral ingestion of ferrous sulfate at dosages ranging from 40 to 1600 mg./kg., with an average value of approximately 900 mg./kg. of ferrous sulfate. Comparing this value with those found for the fatal dose of ferrous sulfate in experimental animals it is apparent that this is considerably smaller than the acute oral toxicity value given for the mouse (4500 mg./kg.), guinea pig (1500 mg./kg.) and rabbit (3000 mg./kg.) and of approximately the same magnitude as that given for the cat (>500 mg./kg.) and the dog (800 mg./kg.). It will be noted, of course, that the figure, 900 mg./kg., is based largely on ferrous sulfate poisoning in cases approximately 2 years old and younger. Further consideration of the relative toxicity of ferrous sulfate in man and animals will be taken up again in the presentation of the experimental data from this laboratory[38].

Probable Toxicity Mechanisms. Various mechanisms have been postulated in an effort to explain the cause of death in cases of poisoning following the oral ingestion of iron salts[18,43,58,66,72]. It is difficult to establish that any one factor is solely responsible. Mounting evidence tends to bring into focus the role of the gastrointestinal irritation observed following the fatal ingestion of these preparations. The severe nausea, hematemesis, abdominal cramps and diarrhea followed by the development of profound shock all tend to point to the potentially corrosive effects of these salts as a starting point in the chain of events which leads to a fatal outcome. It has been suggested that the initial effect is a direct corrosion of the gastric mucosa which results in excessive absorption of iron into the systemic circulation with the formation of apoferritin. This then combines with the iron to form ferritin[66], the substance thought to be identical with the vasodepressor material (V.D.M.) found in the blood of animals in experimentally induced shock.

Although vomiting does occur in the human, it does not seem especially reliable as a protective mechanism in iron poisoning. Particularly in young children, the rapidly developing tissue

destruction following the ingestion of large amounts of ferrous salts appears to interfere with these efforts to rid the stomach of massive quantities of iron, often with fatal results. This factor should tend to emphasize the importance of *prompt* and *gentle* gastric lavage combined with vigorous supportive therapy for shock in suspected poison cases. Further, it should stimulate the search for less irritant forms of iron for oral medicinal use.

Summary. The literature on the toxic effects of iron compounds in man and animals is reviewed. The oral median lethal dose in different species has been approximated from published data for the common iron salts. In addition, an estimated fatal dose for humans has been calculated from cases of ferrous sulfate poisoning. Probable mechanisms of toxicity are discussed.

Conclusions. 1. There are adequate data in the literature to establish conclusively that iron salts are toxic to both man and animals. Of 78 cases of poisoning reported in man, 30 ended fatally.

2. The oral toxicity of iron compounds is not a function of the iron content alone, but is dependent upon the particular salt as well.

3. The majority of reported poisonings in man are due to ferrous sulfate. Of the 63 cases reported as due to this salt, 23, or more than one-third, ended fatally. From these data the fatal dose of ferrous sulfate in humans is estimated to be approximately 900 mg./kg.

4. A smaller number of cases of poisoning have been reported after the ingestion of ferrous chloride, ferric chloride and ferric ammonium citrate.

5. No cases of poisoning have been reported from ingestion of ferrous gluconate.

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RADIOLOGY

UNDER THE CHARGE OF

DAVID M. GOULD, M.D.
ASSOCIATE PROFESSOR OF RADIOLOGY
THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL

AND

JOHN G. MCAFEE, M.D.
ASSISTANT PROFESSOR OF RADIOLOGY
THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL
BALTIMORE, MARYLAND

THE LOBES AND INTERLOBAR PLEURA: FUNDAMENTAL ROENTGEN CONSIDERATIONS

BY BENJAMIN FELSON, M.D.
PROFESSOR AND DIRECTOR, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE AND THE CINCINNATI GENERAL HOSPITAL, CINCINNATI, OHIO

CHEST Roentgen interpretation should not merely represent an attempt to correlate particular shadows with specific diseases, but should be approached with some understanding of the basic principles of anatomy, physiology, pathology, and radiology involved. The application of these principles often increases the accuracy of film interpretation. For example, familiarity with the pathological appearance of Friedländer's pneumonia enables one to suspect this disease when lobar enlargement is encountered on the roentgenogram.

Certain salient facts regarding the pulmonary lobes and interlobar pleura are not well known, while other widely accepted beliefs are fallacious. The purpose of the present publication is to describe some of the basic concepts relating to these structures and to illustrate their practical value and shortcomings under actual working conditions.

Roentgen Anatomy and Variations (Fig. 1). The normal interlobar pleural septa or fissures are often seen on chest roentgenograms, but seldom in their entirety. They may be anatomically incomplete, or obscured by superimposition of ribs or other structures. Normal and pathological variations of the lobar contours may also interfere with their visibility. The septa are best demonstrated on Bucky films and are less clearly depicted on improperly centered roentgenograms and those of low contrast. Their average thickness is about 0.2 mm.

The location of the septa in relation to the chest wall is quite variable. They seldom extend as high as usually stated in anatomy texts, which are based on postmortem studies. In the lateral view the upper posterior extent of the oblique or major septum usually lies at the level of the vertebral end of the fifth rib or fifth interspace, the right side often slightly lower than the left. The oblique fissure usually parallels the sixth rib and reaches the diaphragm several centimeters behind the anterior costophrenic angle. It presents a smooth flat or gently curved surface. In the frontal view it is not normally visible because the Roentgen-ray beam does

not strike it tangentially. Only when considerable pathological displacement downward has occurred is it seen in this view. The major fissure is said to be incomplete in about 30% of anatomical dissections[10].

the junction of the horizontal with the oblique septum is visualized, the right major septum is, of course, readily identified. It is often possible to differentiate the right from the left hemidiaphragm on the lateral view by the

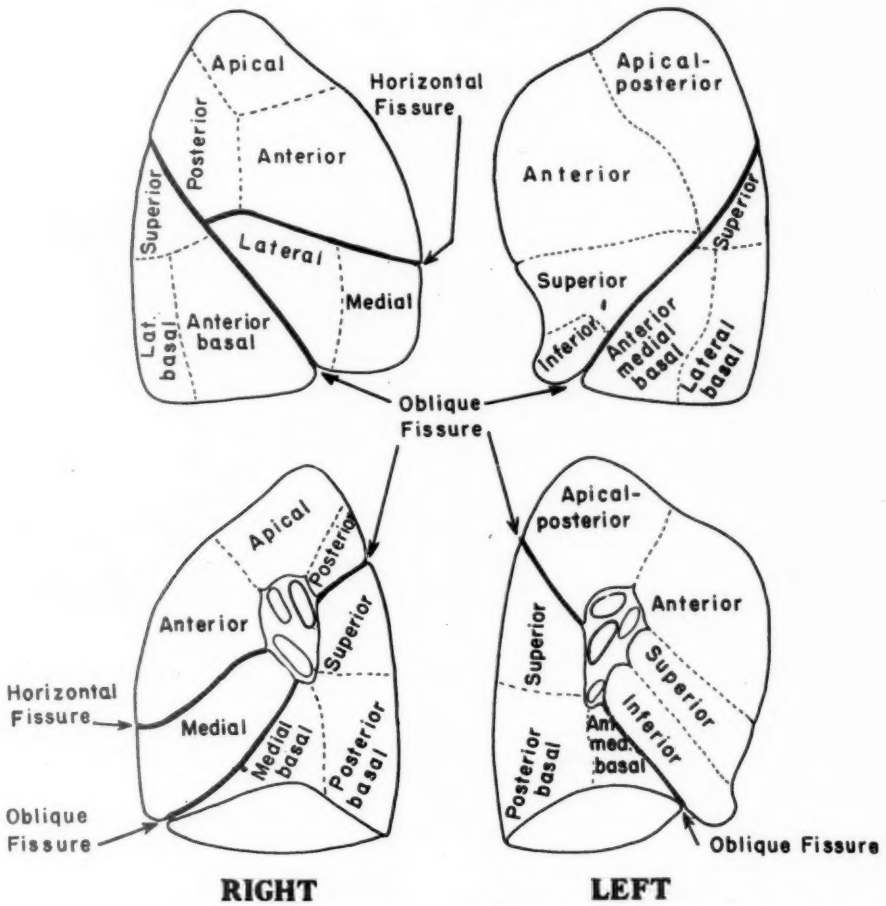

Fig. 1.—Diagram of the bronchopulmonary segments and interlobar fissures in lateral aspects (above) and mediastinal aspects (below). Taken from **Jackson, C. L., and Huber, J. F.,** Dis. Chest, **9**, 1, 1943 (with permission).

Portions of both right and left major septa can often be clearly delineated on a single lateral roentgenogram, and the two may be confused. The septum on the side nearer the Roentgen tube is not usually quite as distinct as that on the side closer to the film. If

position of the gastric air bubble or inferior cardiac border, thus enabling one to recognize each major septum by its junction with the corresponding diaphragm (Fig. 2). If necessary, oblique or stereoscopic lateral views can be obtained for clarification.

As with the major septum, there is considerable variation in the position of the normal right minor or horizontal septum. In the lateral roentgenogram it usually meets the oblique septum in the midaxillary line at the level of the fifth rib or interspace. It is often not truly horizontal but gently curved, with convexity upward. It reaches the anterior chest wall at a variable level, usually near the anterior end of the fourth rib[4,16]. The minor fissure has been found absent or insignificant in 25% of anatomical dissections. It is visible on posteroanterior roentgenograms in 44% of adults and 15.5% of children, according to Hilgert[15]. The middle lobe varies in size, depending on the location of the junction of the minor and major septa. This point may lie well above or below the midpoint of the major septum.

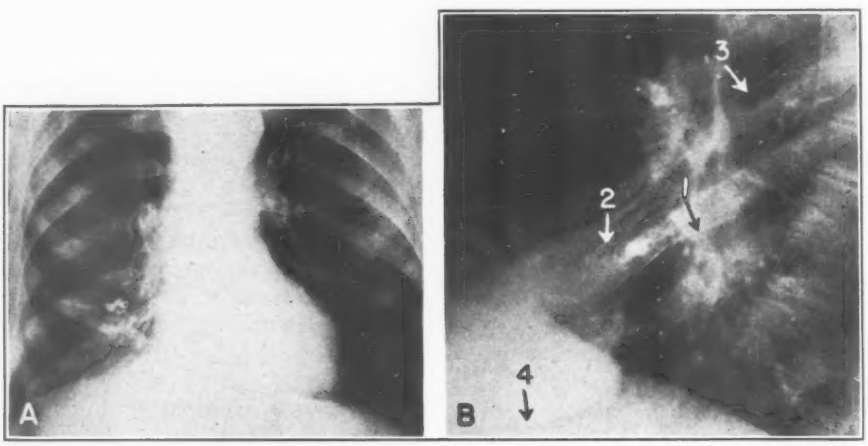

Fig. 2.—Collapse of right lower lobe (broncholith). Note crowded vascular markings in *A*. The hilum is slightly depressed and the diaphragm is slightly elevated. In the right lateral view (*B*) the lobe appears radiolucent. The right major septum (1), identified by its junction with the minor septum (2), is displaced posteriorly. The left major septum (3) is also visible. The lower border of the heart shadow (4) indicates the position of the left diaphragm.

Anomalous septa are not uncommon and can often be recognized roentgenographically. The best known of these is the azygos fissure which subtends a variable amount of the medial superior portion of the right upper lobe, forming the azygos lobe. It is present in 1% of anatomic specimens and is visible in about 0.4% of chest roentgenograms[14]. The site of this fissure bears no constant relationship to the anatomic segments of the lung, a situation contrary to that found with other anomalous fissures. A left azygos lobe is encountered as an extremely rare anomaly[3,24]. Monod[18] observed a specimen with a fissure for the subclavian artery.

The superior segment of the right or left lower lobe may be separated from the remainder of the lobe by a substantial incisura or even a complete septum, and form a *superior accessory lobe*. This occurs in about 5% of anatomic specimens and is considerably more common on the right. Not infrequently the septum can be demonstrated roentgenologically as a horizontal pleural line. In the frontal view it is seen at the approximate level of the

minor septum, and is often mistaken for it. In the lateral view, however, it extends backward from the major septum to the posterior pleural surface. In this projection it often appears to be a posterior continuation of the minor septum, the two forming an *X* with the major septum. Consolidation in a superior accessory lobe presents a sharp lower border on the frontal roentgenogram and may be mistaken for upper lobe disease, especially when it occurs on the right side. Similarly, the upper border of infiltrate in the basal segments of the lower lobe may be sharply demarcated by the anomalous fissure, thus simulating middle lobe disease. Since this lobe is not anatomically contiguous with the heart, its opacification does not result in the obliteration of the heart border seen with middle lobe disease[6]. The localization is readily confirmed in the lateral view.

In about one-third of anatomic dissections an incisura separates the lateral border of the medial basal segment from the remainder of the basal segments of the right lower lobe[10]. Not infrequently this separation is pronounced and the septum is visible on the frontal roentgenogram as an oblique line near the right cardiophrenic angle. The segment thus outlined is called the *inferior accessory lobe*. In the lateral projection the Roentgen-ray beam strikes perpendicularly to the flat surface of the septum so that the fissure is not seen. Since the medial basal segment is seldom an anatomic unit in the left lower lobe[10], an inferior accessory lobe on the left side must occur very rarely, if at all.

As stated earlier, the minor fissure is absent or insignificant in about 25% of anatomic specimens. However, in these cases the segmental anatomy is normal, and middle lobe consolidation still presents roentgenographically with a fairly sharp upper border. Rarely, the right middle lobe bronchus arises from the right upper lobe bronchus, and mirrors the lingula of the left lung.

Boyden[2] described a left middle lobe separated from the upper lobe by an anomalous minor fissure, often incomplete, in 8 of 100 anatomic specimens. Another variation, exceedingly rare, is a third lobe of the left lung supplied by a bronchus arising from the main stem[14]. It should be noted that *any* bronchopulmonary segment or subsegment may, in rare instances, be separated from its neighbors by a fissure[10]. Occasionally an anomalous bronchus arises directly from the trachea and extends into the right upper lobe. Whether or not it supplies a supernumerary lobe demarcated by pleura is not clear from the literature[11].

Sequestered lung is a mass of anomalous lung tissue which is not connected with the bronchial tree and has its own arterial supply from the aorta. Intralobar sequestration almost invariably develops within the substance of a lower lobe in the region of the posterior basal segment, and in these cases the anomalous tissue is usually enclosed within the pleura of the affected lobe. Extralobar sequestration is found either below the diaphragm or between the diaphragm and the lower lobe, and is enclosed in a pleural sheath of its own[5]. Anomalous pulmonary masses which communicate with the trachea, esophagus, or stomach have also been reported[1].

Lobar Collapse. The term collapse is herein used to indicate a diminution in volume of a lung, lobe, or segment from any cause. Although collapse sometimes results from fibrosis with contraction, and from extrinsic pressure (for example, pleural effusion), the discussion which follows will be concerned only with the so-called "obstructive" form.

Obstruction of a lobar bronchus may

occur in many dissimilar conditions. These fall into four main categories*: (1) intrinsic mass lesions, such as primary and metastatic neoplasm** and eroding lymph nodes; (2) intrinsic stenosis, from tuberculosis or other inflammatory processes; (3) extrinsic pressure, as by enlarged lymph nodes, mediastinal tumor, aortic aneurysm, and cardiac enlargement†; and (4) bronchial plugging, as by foreign material and mucus accumulation.

There are many instances of lobar collapse in which the lobar bronchus is widely patent, as revealed by bronchoscopy or bronchography (Fig. 5B). Various theories have been offered to explain this form of collapse. In our opinion, the best of these is that innumerable obstructions by secretions or inflammatory swelling occur in the smaller bronchi and result in collapse of the entire lobe. Fleischner[9] has called attention to the invariable absence of bronchographic filling of the finer twigs of the bronchial tree in bronchiectasis (Fig. 5). We have noted, with few exceptions, a similar failure of bronchographic filling of the smallest divisions of the bronchial tree in lobar collapse unassociated with bronchiectasis.

This peripheral form of obstructive collapse is also encountered in a wide variety of conditions. It is quite common in lobar pneumonia, particularly during the stage of resolution, and is seen in primary atypical pneumonia, and in the pneumonias complicating pertussis, diphtheria, and measles. It frequently occurs in bronchiectasis, kerosene aspiration, the pulmonary involvement associated with cystic fibrosis of the pancreas, and early in the course of radiation pneumonitis.

The most direct and reliable Roentgen sign of lobar collapse is the diminished volume of the lobe as shown by the position of its septa. The degree of collapse varies, but it is seldom complete because of the inflammatory changes usually associated with the obstruction. The term *drowned lung* has been applied to the extensive inflammation and edema which often occurs distal to an occluded major bronchus.

Radiopacity of the affected lobe, reflecting the loss of aeration invariably present, is another direct Roentgen sign of collapse. This sign is not always apparent on conventional frontal and lateral roentgenograms (Figs. 2 and 6), and sometimes lordotic or oblique views are required for its demonstration.

When an airless portion of lung is anatomically contiguous with a border of the heart, great vessels, or diaphragm the normal sharp outline of that border on the roentgenogram will be lost. This occurs because the normal Roentgen visibility of these structures depends on the presence of air in the adjacent lung. We have termed this blurring of borders the *silhouette sign*[6] and have found it particularly useful in detecting loss of aeration in lobar collapse. In right middle lobe collapse, for example, the frontal view (and sometimes even the lateral view) may show little or no evidence of the airless lobe. However, the right border of the heart is almost invariably obliterated in such cases. When the right cardiac silhouette is

*Traumatic fracture of a bronchus might be considered a fifth category.

**Hypernephroma not uncommonly metastasizes to the wall of a bronchus.

†We have encountered a number of instances of lobar collapse caused by cardiac enlargement, specifically in rheumatic mitral stenosis, endocardial fibrosis, atrial septal defect, and patent ductus arteriosus. In our material the left lower lobe was almost invariably involved, either alone or in conjunction with the left upper lobe.

partly or completely lost, additional views to confirm or disprove the presence of collapse are indicated (Fig. 3). Similarly, in lower lobe collapse the opacity of the affected lobe is sometimes only visible in the frontal view. The loss in outline of a segment of rounded by airless parenchyma and their air-filled lumens stand out in contrast. This phenomenon has been called the *air bronchogram* by Fleischner[8], and is often seen in pulmonary consolidation from any cause. When it occurs in the presence of collapse, the bronchi

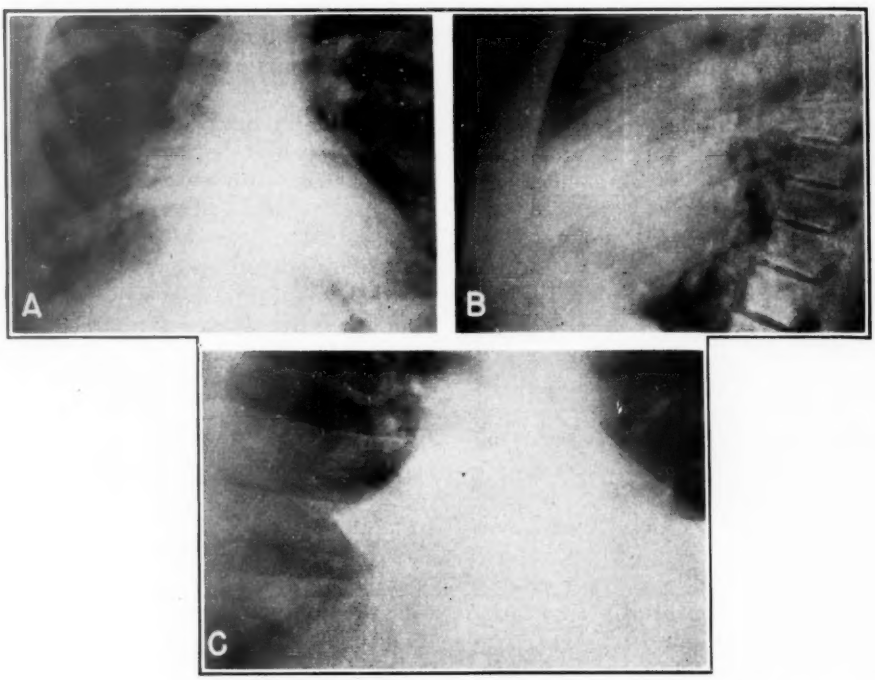

Fig. 3.—Right middle lobe collapse ("middle lobe syndrome"). *A.* Obliteration of the right heart border is the only evidence of the airless lobe. *B.* Right lateral view normal (middle lobe is obscured by heart and breast shadows). *C.* Lordotic view reveals the wedge-shaped shadow of the collapsed middle lobe.

diaphragm in the lateral view may then help to establish the location of the pathological process (Fig. 4).

If vascular markings are visible in a collapsed lobe which still contains some air, they will appear crowded together (Fig. 2A). Divisions of the lobar bronchus, normally invisible on the roentgenogram, sometimes appear as branching linear shadows of air density in the opacified lobe. The bronchi are visible because their walls are sur-

appear to lie close together (Fig. 5). It is encountered much more frequently with the peripheral form of collapse than with obstruction of a lobar bronchus since in the latter the smaller bronchi are usually airless.

The *primary* signs of lobar collapse, then, include displacement of the fissures, loss of aeration, and crowding of the vascular and bronchial markings. The *secondary* signs of lobar collapse include unilateral elevation of the dia-

phragm, shift of the mediastinal structures toward the side of the affected lobe, narrowing of the thoracic cage, compensatory emphysema of the uninvolved lobes, and hilar displacement. Of these, the last mentioned is the most reliable, but none of the secondary signs are, in themselves, conclusive evidence of collapse.

Unilateral elevation of the diaphragm is seldom encountered in collapse of the upper and right middle lobes, and is not even a constant finding in lower lobe collapse. Furthermore, diaphragm elevation is not only a common feature of many abdominal and thoracic conditions unassociated with collapse, but is also often encountered in the normal patient. The author recorded the diaphragm levels in 500 normal posteroanterior teleoroentgenograms of the chest (army inductees) and found that 11% had a significant degree of unilateral elevation, 2% on the right and 9% on the left.

Deviation of the trachea is commonly, but not invariably, seen in upper lobe collapse (Fig. 6B). It is infrequent in collapse of the lower or middle lobes. It is seen also in association with scoliosis, pleural disease, and fibrotic apical lesions. Poor positioning of the patient in the frontal roentgenogram is a common cause of *apparent* displacement of the trachea. Among another group of normal inductees, 100 posteroanterior teleoroentgenograms showing minor degrees of patient rotation were studied. In two-thirds of the cases the rotation was toward the right anterior oblique position (right shoulder closer to the film) as determined from the fact that the medial end of the left clavicle lay further from the spine than that of the right. In this group the trachea was located to the left of the midline of the spine in 39%, to the right of the midline in 3%*, and in the midline in 57%. In the remaining one-third the rotation was toward the left anterior oblique position, and in these cases the trachea lay to the right of the midline in 30%, to the left of the midline in 1%, and in the midline in 70%. Of 450 patients in whom no Roentgen evidence of rotation could be detected, 1% showed some degree of tracheal deviation to either the right or left of the midline, without apparent cause. The tracheal deviation in each of these cases was distinct, and equal to that seen in many cases of upper lobe collapse.

Shift of the heart toward the side of the collapsed lobe occurs rather infrequently. Cardiac displacement may, of course, also result from pleural or pulmonary fibrosis, chest deformities, diaphragmatic eventration or hernia, and intrathoracic masses. Occasionally, the heart may lie predominantly in the right thorax without apparent explanation. This represents a congenital malformation which has been termed *dextroversion of the heart*. We have encountered dextroversion in 6 asymptomatic patients, one a newborn infant[23].

Narrowing of the rib cage on the side of the collapsed lobe is an infrequent secondary sign of collapse. It also results from thoracic deformities and pleural or pulmonary fibrosis, and is simulated by slight rotation of the patient during roentgenography.

Evidence of compensatory overexpansion of the lung adjacent to the diseased lobe is sometimes a helpful secondary sign of lobar collapse. This is recognized in the frontal view as an increased radiolucency with spreading of the bronchovascular markings, when comparison is made with the opposite lung (Fig. 4A). With marked degrees

*No explanation for this deviation, which was in the opposite direction to that expected, was found.

of collapse, especially of an upper lobe, the opposite lung may herniate across the midline to fill the space evacuated by the collapsed lobe. While this can usually be demonstrated on frontal and lateral views, it is best seen in the lordotic view[13].

Displacement of the hilum is an important secondary sign of collapse. In most normal roentgenograms the right hilum lies about 1 cm. lower than the left. Not infrequently, however, the two lie at approximately the same level. Sometimes the hilum is obscured by a pathological density and its position becomes difficult to establish. In such cases the hilar level can usually be determined by tracing the vascular markings of the central portion of the lung medially toward their confluence.

Hilar displacement may be the *only* evidence of collapse if the lobe is so shrunken as to be hidden by the mediastinal structures (Figs. 4 and 6). Elevation of the hilum is the usual finding in upper lobe collapse, but hilar depression is not nearly so frequent in collapse of the lower or middle lobes. In fact, hilar displacement is usually absent in middle lobe collapse and in cases of lower lobe collapse in which the diaphragm is elevated. Contracting pulmonary and pleural fibrotic processes may, of course, cause hilar displacement. This is particularly striking in some cases of chronic fibroid apical tuberculosis, in which the hilum is so elevated that the vascular markings emanating from it travel vertically downward to the lower lobe.

Many excellent descriptions of the detailed Roentgen findings in collapse of the individual lobes are available, including those by Robbins and Hale[21], and Lubert and Krause[17]. This phase of the subject will, therefore, receive only brief consideration here.

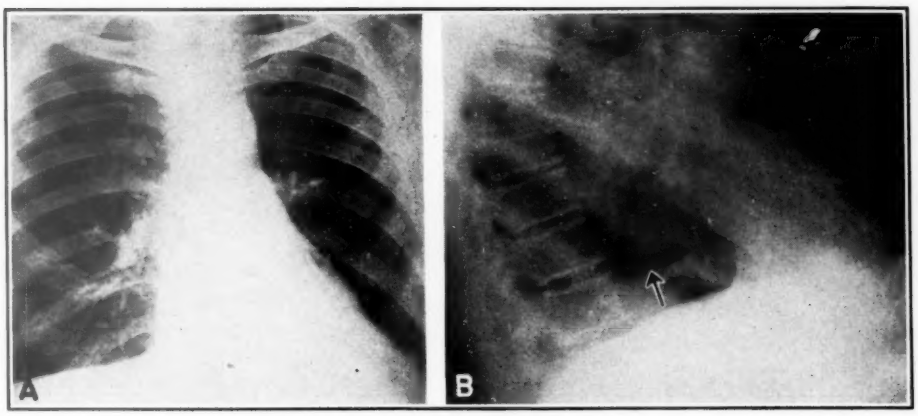

Fig. 4.—Collapse of left lower lobe (carcinoma). *A*. There is compensatory emphysema of the left upper lobe, but the collapsed lower lobe is obscured by the heart. *B*. The lower lobe appears radiolucent in the left lateral view, but it obliterates the posterior portion of the left diaphragm shadow (arrow).

The lower lobe collapses downward, posteriorly, and medially toward the spine, retaining its connection with the hilum through a tongue of opaque lung tissue which has been called the mediastinal wedge[17].

In the frontal view the radiopacity of the affected lobe is usually clearly visible. However, with marked collapse,

especially of the left lower lobe, it may be hidden by the heart density (Fig. 4A). In this situation well-penetrated films usually reveal the airless lung through the cardiac shadow, the heart on the affected side appearing denser than on the normal side[20]. In lower lobe collapse the heart border is not obliterated. The minor septum may be displaced downward, but more often retains its normal position. With considerable collapse the major septum may be displaced downward and medially to such a degree that the Roentgen-ray beam strikes it tangentially, producing a sharp supero-lateral border. With partial collapse sufficient aeration may remain to reveal crowding of the vascular markings. If an air bronchogram is visible, the bronchial markings will also appear crowded together (Fig. 5). The frontal view is best for the demonstration of the secondary signs of collapse. The hilar depression and the compensatory emphysema vary with the degree of collapse, and inversely with the shift of the heart, elevation of the diaphragm, and narrowing of the intercostal spaces.

In the lateral view the major septum is displaced posteriorly. This displacement is sometimes detected even before the increased density of the collapsed lobe is recognized (Fig. 2B). The septum may remain straight or show an anterior concavity. The shadow of the diaphragm is lost along the area of anatomic contact with the airless lobe. In fact, the obliteration of a segment of the diaphragm may be the only evidence of loss of aeration apparent in this view (Fig. 4B).

The collapsed right middle lobe and lingula* may cast only a faint shadow on the frontal roentgenogram because of their relatively small anteroposterior diameter. However, they almost invariably obliterate the adjacent heart border, so that the silhouette sign is often helpful in the recognition of collapse of these lobes (Fig. 3). Collapse of the middle lobe is usually associated

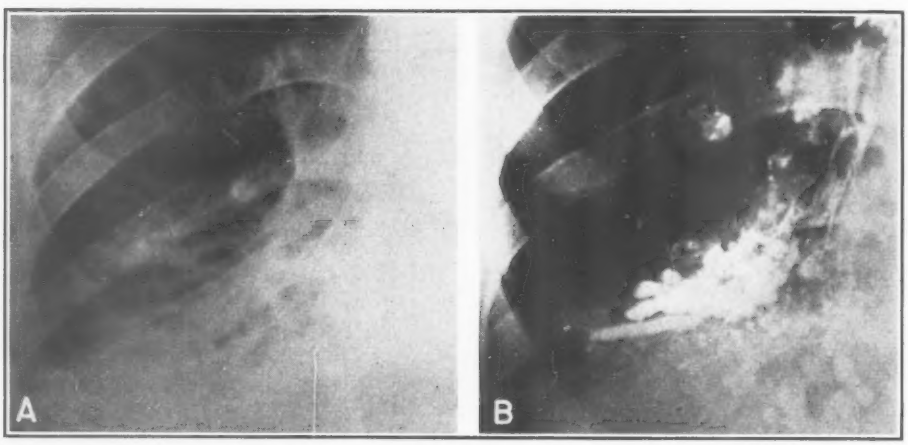

Fig. 5.—Collapsed right middle and lower lobes (bronchiectasis). Note crowding of air-filled bronchi in *A*. The widely patent lobar bronchi are seen in *B*. There is no "alveolar" filling.

*Since the lingula behaves as a counterpart of the right middle lobe it is discussed in this section, rather than with the left upper lobe.

with downward displacement of the minor fissure while lingular collapse, of course, does not offer this helpful diagnostic sign. Secondary signs are usually lacking in collapse of the right middle lobe and lingula.

In the lateral view the minor septum and the lower half of the major septum move closer together in middle lobe collapse, sometimes arching toward each other. With lingular collapse there is forward displacement of the lower half of the major septum.

attention to the collapsed lobe. In the lateral view the superior half of the major septum is displaced forward and often presents a posterior concavity. The radiopacity of the upper lobe may be completely obscured by the ascending aorta and mediastinum in this view.

The left upper lobe collapses anteriorly, paralleling the internal surface of the thorax. In the frontal view the aortic knob shadow is usually obliterated by the airless apical posterior segment which lies adjacent to it. The

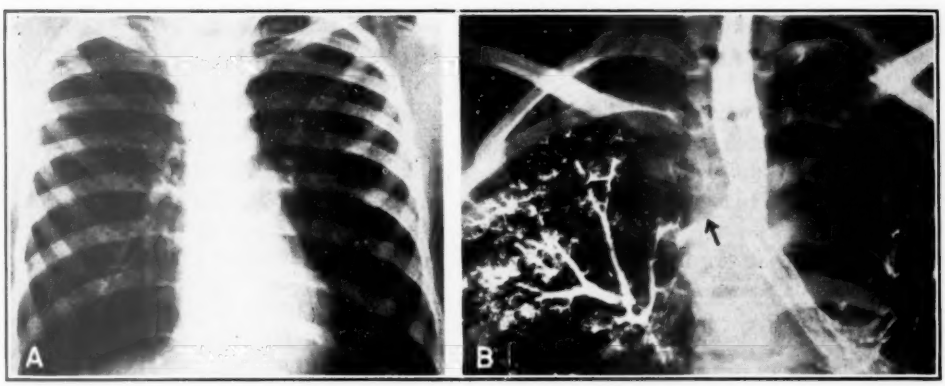

Fig. 6.—Right upper lobe collapse (inflammatory stenosis). In *A* the shadow of the collapsed lobe blends with the superior mediastinum and is easily overlooked. However, the elevated right hilum is a helpful clue. *B*. The bronchogram reveals occlusion of the right upper lobe bronchus (arrow). Note midline position of the trachea.

The Roentgen appearance of collapse of the upper lobes is somewhat different on the two sides. In the frontal view the right upper lobe is displaced superiorly. The minor septum usually reveals a slight downward concavity, the lateral portion showing greater elevation than the medial. This results in a somewhat triangular opacity. With marked collapse this opacity may blend with the right superior mediastinal shadow, and is easily overlooked (Fig. 6). In this event the secondary signs of collapse, especially the elevation of the right hilum, the tracheal shift, and the compensatory emphysema may call

tracheal deviation and hilar elevation are usually striking. Rarely, the emphysematous lower lobe may extend to the apex of the lung and present as a clear area above the collapsed lobe. In the lateral view the major septum is displaced forward and bowed anteriorly, lying parallel to the sternum.

In the Roentgen differential diagnosis of lobar collapse only two conditions need receive serious consideration: (1) consolidation without collapse (for example, lobar pneumonia) and (2) encapsulated pleural fluid. In lobar consolidation septal displacement does not occur and the secondary signs of

collapse are lacking. Pleural fluid encapsulation may simulate collapse closely, especially when situated in the lower posteromedial portion of the pleural cavity, or in an interlobar fissure. In the former location the anterolateral surface of the encapsulation is usually convex, while in lower lobe collapse this surface is concave or straight. In the lateral view the normal major septum is usually visible anterior to the encapsulation, and there is almost invariably evidence of pleural thickening elsewhere in the thorax, particularly in the costophrenic sinus. The differentiation between interlobar encapsulation and middle lobe collapse will be discussed later.

As mentioned previously, there are innumerable causes of obstructive lobar collapse, and it is often impossible to distinguish between them roentgenologically. Nevertheless, there are certain leads that can be obtained from Roentgen studies which may have important etiologic connotations. The presence of enlarged lymph nodes, a foreign body, a mediastinal mass, or cardiac enlargement may be recognized as the cause of the obstruction. Laminagraphy or bronchography may reveal an obstructing or stenosing lesion in the lobar bronchus and, from its configuration, the nature of the underlying disease can often be suspected. Lobar collapse occurring in the absence of a lesion of the lobar bronchus rules out, for all practical purposes, carcinoma of the lung, except for alveolar cell carcinoma[25]. The reverse S-shaped curve seen in the frontal view in some cases of collapse of the right upper lobe has been described as a helpful sign in the diagnosis of carcinoma[12]. The upper lateral concave segment of the S is formed by the elevated minor fissure, and the lower medial convex segment is formed by the tumor mass causing the collapse. However, enlarged nodes or mediastinal tumor with collapse may give an identical appearance. Lobar collapse accompanied by pleural effusion on the same side usually indicates carcinoma.

When certain combinations of lobes are found to be collapsed the diagnosis of carcinoma of the lung becomes extremely unlikely. For example, right upper lobe collapse associated with either middle or lower lobe collapse is rarely seen in carcinoma of the lung. The anatomic take-off of the right upper lobe bronchus is so situated that tumor extending from it must enter the main stem bronchus, and is much more likely to cause collapse of *both* the middle and lower lobes. Similarly, collapse of the lingula and left lower lobe cannot be explained on the basis of a single lesion, since the upper lobe bronchus intervenes between the main bronchi to these lobes. Left upper and lower lobe collapse without lingular involvement is also rarely attributable to neoplasm, and then only when a primary carcinoma of one lobe is associated with metastatic nodes which compress the bronchus to the other.

Lobar Enlargement. Enlargement of an individual lobe is easily recognized roentgenologically by the outward bulging of its septa. Except in the right upper lobe, this requires films made in both frontal and lateral views. Even when a lobe is incompletely consolidated the septum may still bulge if the disease process occupies the segment adjacent to it. Lobar enlargement can be mimicked to a certain degree by encapsulated interlobar fluid, but the latter shows a sharply defined biconvex shadow, whereas lobar enlargement shows a single convex border at the surface adjoining the interlobar fissure.

There are few pathological conditions capable of causing lobar enlargement, and their differentiation is

usually readily made on the basis of the clinical and laboratory findings. In a previous communication[7] lobar enlargement was described in 5 of 8 cases of Friedländer's pneumonia. We have encountered several additional cases of lobar enlargement in this disease since that time. The Roentgen findings are readily explained at the necropsy table by the demonstration of voluminous lobes packed tightly with inflammatory products.

Lobar enlargement is not to be considered a pathognomonic sign of Friedländer's pneumonia, since it is also encountered in a small percentage of cases of pneumococcic pneumonia, tuberculosis, and lung abscess and is not uncommon in carcinoma of the lung. However, its high incidence in Friedländer's pneumonia should enable one to suggest this diagnosis when a bulging septum is encountered in a patient presenting the signs and symptoms of lobar pneumonia.

The Disrupted Septum. The interlobar pleura usually serves effectively as a barrier to the extension of pathological processes from one lobe to another. Although malignant tumors, lung abscess, and tuberculosis sometimes are found to trespass these thin septa at necropsy, this is seldom detectable roentgenographically. Certain fungus diseases, notably actinomycosis and blastomycosis, not infrequently disrupt a portion of the interlobar pleura. Hence, Roentgen evidence of a pulmonary lesion extending directly across a fissure into the adjacent lobe should suggest the possibility of a mycotic infection. Neoplasms arising in or near the main stem bronchus (especially bronchogenic carcinoma and lymphoma) may spread in the walls of the bronchi or vessels and involve several lobes simultaneously. Roentgenographically, this may falsely suggest extension across the fissure.

The fact that neoplasms seldom penetrate the interlobar septa can be utilized as an aid in differential diagnosis. When there is involvement of adjacent lobes or segments that cannot be explained by a single bronchial tumor, one has reasonable assurance that neoplasm is not present. For example, simultaneous involvement of the superior segment of the right lower lobe and the posterior segment of the right upper lobe speaks strongly against carcinoma of the lung, since a single bronchial lesion could not cause this combination, and extension across the fissure is unlikely. Similarly, involvement of the middle lobe and the adjacent basal segments of the right lower lobe would be an extremely rare combination in bronchogenic carcinoma.

Interlobar Effusion. Interlobar encapsulation is not nearly as common as formerly believed. Many cases so diagnosed were, in fact, instances of middle lobe collapse. Encapsulated interlobar effusion is encountered most commonly in cases of congestive heart failure in which the pleural cavity is partially or completely obliterated by adhesions.

Encapsulation in the minor fissure presents itself in the frontal roentgenogram as a sharply defined round or oval shadow in the right midthorax. Because of its Roentgen configuration and rapid disappearance it has been called *pseudo-tumor* of the lung. In the lateral view it appears as a spindle-shaped shadow in the region of the minor fissure, usually associated with thickening of the major septum. The correct diagnosis can be suspected from the location of the density, the slight tapering at its extremities, and the presence of pleural thickening elsewhere in the hemithorax. Localized pleural mesothelioma[22] may simulate this appearance closely but can be ruled out by the changing appearance of inter-

lobar effusion shown on serial roentgenograms.

Encapsulated fluid in the oblique fissure appears in the frontal roentgenogram as a moderately dense, broad, kidney-shaped opacity which is concave medially. It is readily recognized in the lateral view by its configuration, and by its location in the plane of the major fissure.

The distinction between middle lobe collapse and fluid encapsulated in the lower portion of the right major fissure or in the minor fissure may offer considerable difficulty. They are best differentiated on the lateral roentgenogram. In middle lobe collapse ordinarily one border of the density, at least, is concave or straight. A line drawn to bisect the long axis of the radiopacity does not fall in the plane of either the major or minor fissure, as would be the case with interlobar effusion, but lies somewhere in between. If air-filled bronchi or alveoli are visible within the opaque shadow, interlobar effusion can be eliminated from consideration.

Summary. An attempt has been made to apply some basic concepts relating to the pulmonary lobes and interlobar pleura to chest Roentgen interpretation.

Following a description of the Roentgen anatomy, and variations and anomalies of the interlobar septa, an evaluation of each of the direct and secondary Roentgen signs of lobar collapse is made. The Roentgen findings in collapse of the individual lobes are also described.

The subject of lobar enlargement is briefly reviewed in the light of experiences wth Friedländer's pneumonia; disruption of the interlobar pleura by fungus disease is also emphasized. Finally, the Roentgen signs and differential diagnosis of encapsulated pleural effusions are considered.

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

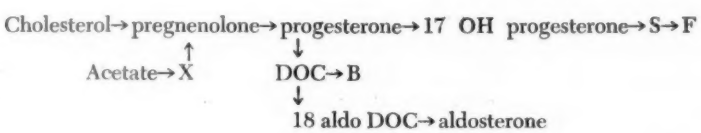
SESSION OF MAY 17, 1955

INFORMAL SEMINAR ON ADRENAL CORTICAL FUNCTION

The Alpha-Ketolic Hormones of the Adrenal Cortex.* E. M. RICHARDSON, PH.D. (Endocrine Section of the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania, and the Department of Medicine, School of Medicine, University of Pennsylvania). Evidence that F, B and aldosterone are the principal alpha-ketolic hormones secreted by the adrenal cortex has come from several sources. The alpha-ketolic steroids A, B, E, F, S and DOC, and aldosterone, all active in carbohydrate or salt regulation, have been isolated from beef adrenals along with 22 other steroids. Perfusion of beef adrenals has resulted in the isolation of 5 of the 7 active hormones, with F and B predominating. This, in conjunction with study of adrenal tissue incubations and partially purified adrenal enzymes has demonstrated the presence of 5 hydroxylating enzymes, a 3β dehydrogenase and an 18 aldolase. The adrenal vein and peripheral blood contain mainly F, B and aldosterone. A scheme for the biosynthesis has been proposed by several authors:

Using paper chromatographic techniques, workers at the University of Pennsylvania have studied the urinary alpha-ketolic metabolites of 6 of the 7 cortical hormones in human subjects with adrenal deficiency. In each case, the principal alpha-ketolic metabolite was the tetrahydro compound of the hormone administered, having the 3α-hydroxy pregnane configuration. They demonstrated the interconvertibility of B and A and confirmed that of E and F. Nine alpha-ketols were found in the urine of normal individuals receiving ACTH. These included F and the tetrahydro forms of E and F, B and A, and their tetrahydro metabolites, including allo tetrahydro B and small amounts of tetrahydro S. This indicated that F or E or both, and B or A or both are secreted by the adrenal cortex. Secretion rates of F and B calculated from the amounts of metabolites agree approximately with the finding of others. Increased excretion of tetrahydro S in adrenal carcinoma suggests that S is secreted due to a block in the conversion of S to F in the cancer cells.

A Metabolic Block in Alpha-Ketolic



*This investigation was supported in part by Research Grant H-922 from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and by a grant from the American Heart Association.

Synthesis. ALFRED M. BONGIOVANNI, M.D., and WALTER R. EBERLEIN, M.D. (Department of Pediatrics, Children's Hospital). A number of patients with the syndrome of congenital virilizing adrenal hyperplasia have been studied. Methods devised by the authors revealed that the excretion of large quantities of 3 alpha, 17 alpha, 20 alpha-pregnanetriol is a constant feature of this disease. Small quantities of this compound (0.5 to 1.5 mg. per day) are excreted by normal adults. The amounts found in the syndrome always exceed the normal range and in affected adults may rise as high as 50 to 60 mg. per day. These findings are associated with the well known elevation of the urinary 17-ketosteroids.

In addition, the levels of circulating 17-hydroxycorticoids have been investigated before and after the intravenous administration of adrenocorticotropin. In 10 of 13 patients studied, there was no elevation of these steroids (presumably Compound F) in the peripheral circulation. This strongly suggests a defective synthesis of Compound F in this condition. In addition, only small quantities of Compounds E, F and their reduced derivatives were found in the urine.

Hechter has proposed a schema for the biosynthesis of Compound F in the adrenal gland based on his perfusion studies. In the last step, 17-hydroxyprogesterone is converted into Compound F. Since pregnanetriol is the reduction product of 17-hydroxyprogesterone and since the patients studied usually exhibit an inability to produce Compound F during adrenocorticotropic stimulation, it appears that there is an enzymatic block in their adrenal cortices at the point in the schema as indicated.

Observations of Adrenal-Deficient Man. A. GORMAN HILLS, M.D., and DAVID W. PARSONS, M.D. (Department of Medicine, University of Pennsylvania). Studies carried out in patients with spontaneous Addison's disease and in 44 clinic patients totally or subtotally adrenalectomized because of hypertensive disease are presented in relation to two questions in the physiology of human adrenal cortical deficiency: 1) the quantitative evaluation of adrenal deficiency and 2) the adequacy of cortisone and desoxycorticosterone as "replacement" therapy.

Following total bilateral adrenalectomy, adrenal insufficiency has invariably ensued (17 patients) upon withdrawal of adrenal steroid therapy; minimum maintenance is somewhat variable but usually amounts to approximately 37.5 mg. of oral cortisone acetate plus 1 or 2 mg. of desoxycorticosterone acetate daily. Following subtotal adrenalectomy (removal of 95% or more of the total adrenal tissue) 8 of 27 patients have required no maintenance steroid therapy, and some others very little. All totally or subtotally adrenalectomized patients tested have exhibited grossly subnormal response to intravenous corticotrophin in terms of augmentation of urinary steroid excretion. The data confirm a conclusion, based on physiologic studies previously reported, that grades of adrenal cortical deficiency can exist which are undetectable by evaluation of adrenal reserve by corticotrophin administration.

Total adrenalectomized man cannot survive without exogenous steroid; patients with spontaneous Addison's disease, like certain subtotally adrenalectomized patients, sometimes can be maintained without steroid, provided adequate sodium chloride is provided in the diet. Minimum maintenance steroid therapy in Addison's disease is comparable with that required after subtotal adrenalectomy and usually less than the requirement of totally adrenal-

ectomized man. It is inferred that some adrenal cortical function is often preserved in spontaneous Addison's disease.

Cortisone can maintain adrenal-deficient man in a state of highly satisfactory well-being in most instances; rarely, supplementation with desoxycorticosterone acetate has been necessary. Cortisone is not, however, ideal or complete replacement therapy, for signs of overdosage in certain respects and of underdosage in others are demonstrable on "physiologic" quantities of this compound. Polyphagia and obesity are overdosage effects; salt-wasting, azotemia and hyperkalemia, and hypoglycemia unresponsiveness, and probably also melanosis and impairment of water diuresis, are signs of incomplete replacement. Melanosis developed in 9 of 27 subtotally adrenalectomized patients, but in only 3 of 17 totally adrenalectomized patients. Intense pigmentation has been seen after subtotal but not after total adrenalectomy.

Mechanism of Cortisone Protection Against Stress. KARL E. PASCHKIS, M.D., A. CANTAROW, M.D., and D. A. DEBIAS (Division of Endocrine and Cancer Research, Jefferson Medical College). Adrenalectomized animals are very sensitive to various injurious agents; administration of adrenocortical hormones restores their resistance to stress. The mechanism by which adrenocortical hormones exert this action is poorly understood. In experiments reported here, adrenalectomized rats were exposed to two forms of stress: cold exposure (2 to 4° C.) and formalin injection. The stressed animals were treated by continuous infusion with compounds, the metabolism of which is believed to be influenced by cortical hormones, and their survival was compared with untreated adrenalectomized animals stressed similarly. Compounds tested include fructose, glucose, with and without insulin, fructose-6-phosphate, adenylic acid, amino acid mixtures, glutamic acid, pyruvate, glutathione, pantothenate, coenzyme A. Partial protection was obtained with glucose, fructose, amino acids plus adenylic acid, pantothenate, and glutathione (formalin stress), and with glucose (cold stress). In view of the possibility that small amounts of cortical hormone might be permissive for utilization, or for entry into cells, of such compounds, the latter were also tested in combination with subprotective doses of cortisone (controls: cortisone treated). In some instances a "synergistic" or "potentiating" action was found. In another series of experiments, the influence of various drugs influencing the autonomic nervous system was studied in a similar way. Pendiomide tartrate partially protected against cold stress; dibenamine and chlorpromazine against formalin stress.

The Biological Properties of Aldosterone. R. GAUNT, PH.D., A. A. RENZI, PH.D., and J. J. CHART, PH.D. (Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.). Although only small amounts of crystalline aldosterone have yet been available, considerable progress has been made in characterizing the hormone biologically. The following conclusions are based on the work of numerous investigators recently reviewed by the authors (J. Clin. Endocrinol. & Metab., **15**, 621, 1955). The renal sodium-retaining effect of aldosterone is some 20 to 100 times that of desoxycorticosterone (DC), the apparent variation depending upon the test employed. It is about 5 times as active as DC in enhancing K excretion. Aldosterone does not affect water excretion when given in the low doses adequate to alter electrolyte excretion; under similar condi-

tions, DC is either without effect or is antidiuretic and hydrocortisone is diuretic. When aldosterone and hydrocortisone are given in doses equal by weight, however, they are equipotent in stimulating diuresis and restoring deficient renal clearances in adrenalectomized rats. In maintaining adrenalectomized dogs and Addisonian patients, aldosterone is 10 to 30 times as active as DC. Doses of 10 μg. will depress the salivary Na/K ratio in man. One milligram per day in man may cause sodium and water retention and expansion of extracellular fluid volume. Long-term overdosage studies are lacking but observations on patients with "primary aldosteronism" suggest that excesses of the hormone cause hypokalemia, hypernatremia and no edema. In protecting adrenalectomized animals against the stress of cold or of water intoxication, the potency of aldosterone approximates that of hydrocortisone or cortisone. In other glucocorticoid tests (liver glycogen deposition, ACTH suppression, eosinopenia) it is one-third the potency of cortisone. Under physiological conditions, however, there may not be sufficient aldosterone secreted to exert these hydrocortisone-like glucocorticoid actions but only enough to affect electrolyte metabolism and related phenomena. The hormone probably has no anti-inflammatory actions. Aldosterone secretion is largely independent of ACTH in the dog and man. Its secretion is affected, however, either directly or indirectly, by the intake of sodium or potassium, or both.

SUMMARIO IN INTERLINGUA

(See page 551 for original article)

Le Tractamento de Hypertension Diastolic per Medio de un Fixe Combination de Drogas Hypotensive

Un fixe combination de *Rauwolfia serpentina,* protoveratrina, e phenoxybenzamina esseva usate in le tractamento de 75 patientes con hypertension. Trenta-octo de illes completava un curso de 6 menses e esseva subjicite a un evalutation detaliate. Vinti-octo del 38 patientes (70 pro cento) exhibiva un responsa satisfacente; 19 de illes (50 pro cento del gruppo de 38) manteneva un normotension uniforme durante le curso therapeutic. Le remanente 10 patientes respondeva dissatisfacentemente o non del toto. Le gruppo consisteva predominantemente de patientes con sever hypertension e hypertensive morbo cardiovascular. Omne le patientes in Gruppo I (classification de Smithwick) respondeva satisfacentemente. Un responsa uniformemente dissatisfacente esseva observate in patientes con azotemia.

Le major avantages del therapia hic describite es le presente: (1) Simplicitate del administration. (2) Minimo de sever reactiones lateral. (3) Alte procentage de patientes con responsas satisfacente, mesmo inter le casos de sever hypertension. (4) Minimo comparative de risco, debite al retardation del reduction in pression sanguinee post le initiation del tractamento e al lente retorno al pression sanguinee de controlo post le cessation del tractamento. Le major disavantages es: (1) Alte frequentia de minor sed vexante reactiones lateral. (2) Non-responsa de un considerabile minoritate de patientes, combinate con le impossibilitate de predicer le character del responsa in le majoritate del casos.

BOOK REVIEWS AND NOTICES

CLINICAL APPROACH TO JAUNDICE. By LEON SCHIFF, M.D., PH.D., Prof. of Clinical Medicine, University of Cincinnati College of Medicine. Pp. 107; 52 ills. Springfield, Ill.: Charles C Thomas, 1954. Price, $3.75.

IN a small monograph on the clinical approach to jaundice, Dr. Schiff has presented a short but excellent discussion of an important and what is not infrequently a difficult diagnostic problem. This monograph should be especially useful to the general practitioner in that it presents a survey of the various diagnostic methods useful in the jaundice problem including a group of excellently reproduced photographs from needle liver biopsies. A good history and physical examination in a patient with jaundice are, of course, essential and will often indicate the type of jaundice, whether medical or surgical. Unfortunately, all too frequently, however, such a history and physical examination will leave one entirely in the dark as to the underlying type of jaundice one is dealing with. It is in this group, particularly, that the practitioner should be aware of what the ancillary procedures, such as liver function and needle liver biopsy have to offer and particularly their limitations. The small monograph of Dr. Schiff can serve as excellent reading matter for such a purpose. H. S.

SHOULD THE PATIENT KNOW THE TRUTH? Edited by SAMUEL STANDARD, M.D., and HELMUTH NATHAN, M.D. Pp. 160. New York: Springer Publishing Company, 1955. Price, $3.00.

THIS book was written by 24 doctors, nurses, clergymen and lawyers. It is a thoughtful, human, honest book that every medical student and physician could profitably read some time early in his career. It is at once wise and practical. It challenges one to put the patient's feelings and his problem first and makes clear that skill in doing this varies greatly from patient to patient. Furthermore, it deals quite precisely with how to tell the truth, how to time the telling, what should be withheld and why, as well as how to help the patient deal with the truth of his illness. Cancer and heart disease are given principal attention but other diseases are considered and the application of principles expounded here will apply widely. The contributions of the clergy as well as that of nurses, physicians and lawyers all seem to focus on the emotional and physical welfare of the patient. The cruelty of evasion is made clear and techniques for its avoidance are made more simple and understandable.

O. E.

MYOCARDIAL INFARCTION. By IRVING S. WRIGHT, M.D., CHARLES D. MARPLE, M.D., and DOROTHY FAHS BECK, PH.D. Pp. 656; 192 ills. New York: Grune & Stratton, Inc., for the American Heart Association, 1954. Price, $8.50.

THIS book is a report of the Committee on Anticoagulants which was created by the American Heart Association and reflects the Committee's findings on a study of 1,031 cases. There are thirteen chapters covering the background, origin, purpose, and plan of study by the Committee through an analysis of the signs, symptoms, physical findings, treatment, and necropsy findings of control and treated groups of patients. The material presented is organized and summarized into numerous tables and graphs which give a quick analysis of the many points in question. The evaluation of the effect of anticoagulants by analysis of a control and treated group is the main theme of the book. There are many references made to other works which the Committee utilizes in its presented findings. Essentially, the report acts as an excellent reference on the subject and seems quite complete. G. M.

VITAMINS IN THEORY AND PRACTICE. By LESLIE J. HARRIS, SC.D., D.SC., PH.D., Director, Dunn Nutritional Laboratory, University of Cambridge and Medical Research Council. 4th ed.; Pp. 366; 103 ills. New York: Cambridge University Press, 1955. Price, $6.50.

THIS interesting treatise on vitamins presents the story of these essential food factors in a fashion which will appeal not only to the scientist, but also to the lay reader. This is accomplished by providing the historical backgrounds of deficiency diseases, the steps involved in learning their respective origins and the discovery of the vitamins used in their correction. The evaluation of the nutritional status of the individual for specific vita-

mins is described briefly without a description of techniques or detailed methods. Each vitamin is discussed from the standpoint of biologic actions, availability in various foods and its significance in human and animal nutrition. The final chapter of this excellently illustrated book is entitled *Dietetics—What to Eat* in which the author has provided an enlightened theme for those engaged in portraying the importance of good nutrition to the general public. C. S.

THE ADULT-CHILD INTERACTION TEST: A PROJECTIVE TEST FOR USE IN RESEARCH. By THERON ALEXANDER, Florida State University. Pp. 40; 8 test cards. Champaign, Ill.: Child Development Publications, 1955. Price, not given.

THE Adult-Child Interaction Test is a new projective test aimed primarily at gaining information concerning the social relationship between adults and children, giving this problem a sharper focus than found in other projective tests. This short monograph, which introduces the ACI, gives instructions for administration, a method for analyzing the data, and 2 cases illustrating the use of the test. The application of the ACI for research in such areas as education and situations involving interaction with authority is stressed; however, its clinical applications, although not sufficiently validated at the present time, are also apparent.

Probably the main contribution of this test is the method of analysis which, although recognizing the totality of individual functioning, attempts to describe the performance in terms of apperception and reasoning, motivation and emotion. This method provides a valuable organization of data which might profitably be extended to other projective tests. O. E.

CEREBROVASCULAR DISEASE. By J. PETER MURPHY, M.D., Assistant Clinical Professor of Neurological Surgery, George Washington University. Pp. 408; 128 ills. Chicago: The Yearbook Publishers, Inc., 1954. Price, $12.00.

DOCTOR MURPHY has written a timely book. Cerebrovascular disease is the third most frequent cause of death in the United States. The development of techniques for determining cerebral blood flow, the perfection of cerebral angiography and its use in locating cerebral aneurysms as well as occlusive disease of the cerebral arteries and veins and the perfection of techniques in anesthesia and neurosurgery for the treatment of these intracranial vascular lesions have created a new and vigorous interest in the diagnosis and treatment of these lesions.

The book is well balanced, clearly illustrated and covers every aspect of the subject from embryology of the vasculature to home care of the patient. The chapters are short and to the point. The book will be particularly valuable to the general practitioner and medical student. However, the neurologist and neurosurgeon will find in this book valuable references to many recent neurophysiological and clinical advances in this field. M. S.

POLIOMYELITIS. World Health Organization Monograph Series No. 26. By ROBERT DEBRÉ and 16 contributors. Pp. 408; 69 ills. Geneva: World Health Organization, 1955. Price, $8.00.

THIS monograph, the twenty-sixth of a series prepared under the auspices of the World Health Organization has been written by seventeen American and European experts on poliomyelitis. The mongraph is divided into five sections, which deal respectively with the epidemiology, clinical aspects, virology, immunology, and control of poliomyelitis.

The book contains a large amount of information in its concisely presented material. This monograph will be of interest and usefulness to anyone concerned with any of the above-mentioned phases of poliomyelitis. R. H.

MANAGEMENT OF ADDICTIONS. By EDWARD PODOLSKY, M.D. Pp. 413. New York: Philosophical Library, 1955. Price, $7.50.

THIS book contains articles by various authors on the many different treatment approaches to the problems of alcohol and drug addiction. Among the treatments covered for alcoholism are those utilizing endocrines, calcium, barbiturates, Antabuse, Tolserol, conditioned-reflex therapy, psychotherapy, and hypnotherapy. There are other discussions on drug addiction and in addition to hospitalization, withdrawal and psychotherapy, the use of Benadryl, prolonged sleep and electro-convulsive therapy also are described. It may be difficult for the nonpsychiatrist to decide which treatment method will be most suitable for his patient but he will see the difficulties inherent in treatment of these conditions. He will recognize, further, that in the absence of a single specific thera-

peutic agent for all cases one must use that which best meets the needs of the patient and the environment in which he lives.

O. E.

LIVER INJURY. Transactions of the Twelfth Conference, September, 1953. Princeton, N. J. Josiah Macy, Jr. Foundation. Edited by F. W. HOFFBAUER, M.D. Pp. 193; 52 ills. New York: Josiah Macy, Jr. Foundation, 1954. Price, $4.25.

THE report of the Twelfth Conference on Liver Injury sponsored by the Josiah Macy, Jr. Foundation, while it represents the last of this series of conferences is to this reviewer one of the best of the entire series. This conference was concerned with carbohydrate, fat and protein metabolism and its published reports should make a valuable addition to the library, not only of one primarily interested in liver disease but to any one concerned with nutrition, endocrinology or diabetes. While the informality mentioned in the introduction by Dr. Frank Fremont-Smith, the medical director of the Foundation, is certainly achieved in the discussions, in the published reports this informality and their tempo does not always make for easy reading, since the commentator, speaking to a group of experts should and does take many facts for granted, which limits the appeal of these reports for the general reader.

H. S.

METHODS FOR EVALUATION OF NUTRITIONAL ADEQUACY AND STATUS. Edited by H. SPECTOR, M. S. PETERSON, and T. E. FRIEDEMANN. Pp. 313; 155 ills. Washington: National Academy of Sciences—National Research Council, 1954. Free on request to Quartermaster Food and Container Institute for Armed Forces, 1819 West Pershing Rd., Chicago 9, Ill.

THIS symposium, sponsored by the Quartermaster Food and Container Institute and the Medical Nutrition Laboratory, Office of the Surgeon General, is concerned mainly with the evaluation of the nutritional adequacy of the normal adult population. Among the participants in the symposium are many of the foremost authorities in the field of nutritional research, each contributing a facet to a remarkably complete survey of the relationship of food requirements and composition to body structure and function. The essayists include those engaged in basic biochemical and enzymatic research as well as clinicians whose contributions are of a practical tenor. An important contribution is the discussion of the use of certain experimental animals for the determination of the physiological adequacy of nutrients. The fundamental studies evolving in the measurement of body compartments by various techniques as an index of nutrition is the subject of a round-table discussion which concludes the work. These proceedings should be carefully read by nutritionists, biochemists, physiologists and others interested in research or clinical investigation involving nutrition.

C. S.

PSYCHOTHERAPEUTIC INTERVENTION IN SCHIZOPHRENIA. BY LEWIS B. HILL, M.D. Pp. 216. Chicago: University of Chicago Press, 1955. Price, $5.00.

THIS is a book on the person to person treatment of our most serious mental illness. It describes in a readable way the emotional problems of the schizophrenic, his loneliness, isolation and difficulty in trusting others and tells how this must be met and dealt with in order to bring about improvement. This is one of the best treatises of a highly specialized area of medical endeavor and should be of interest even to the nonspecialist in psychiatry.

O. E.

FLUOROSCOPY IN DIAGNOSTIC ROENTGENOLOGY. BY OTTO DEUTSCHBERGER, M.D., Assistant Clinical Professor of Radiology, New York Medical College. Pp. 771; 888 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $22.00.

THIS sizable new work is unique in its emphasis. As the author points out in his preface, it is the first attempt to bring together a summary of the technical aspects of fluoroscopy and a detailed description of the application of fluoroscopy in the examination of the various body systems.

The author actually describes in more or less detail the techniques and findings of radiographic examination as well as the fluoroscopic approach so that the book really constitutes a one-volume text on diagnostic roentgenology.

It seems to this reviewer that the book somewhat distorts the picture of the present role of fluoroscopy in Roentgen diagnosis. The author properly emphasizes the fact that visual acuity is still so poor with the conventional fluoroscope that final diagnosis, with the possible exception of the heart, must today always rest with the technically adequate radiographic film. While the author frequently

points out the limitations of the fluoroscopic method, the use of this book as one's only guide may conceivably lead to a false sense of security as far as the reliability of deductions made from the fluoroscopic examination alone is concerned.

The book is well organized and well illustrated with diagrams and radiographs. There is a very complete bibliography, including particularly references from the European literature. Many rather fine points in fluoroscopic and radiographic diagnosis are mentioned which seem to be of questionable value and which would certainly require considerable personal evaluation in practice by anyone following the suggestions of the text in detail.

From the point of view of future developments anticipated in diagnostic roentgenology, the appearance of a work emphasizing the role of fluoroscopy is timely. The author has ascribed, in the introductory material on the physical aspects of fluoroscopy, the development of the new fluoroscopic image intensifiers which increase the visibility of fluoroscopic detail to a level something approaching that in a radiograph without the necessity for dark adaptation. However, the application of such image amplifiers in the immediate future will be on such a limited scale that the emphasis in the present volume seems certainly to be premature as far as most physicians are concerned.

Considering the author's thesis that the case for fluoroscopy has previously been understated, the volume is well done and noteworthy. The reviewer feels that the same information is available with better balanced emphasis in many standard works on diagnostic roentgenology which properly evaluate the relative role of fluoroscopy and radiography.

H. S.

A Textbook of Neurology. By H. Houston Merritt, M.D., Professor of Neurology, Columbia University. Pp. 746; 181 ills. Philadelphia: Lea & Febiger, 1955. Price, $12.50.

This is a textbook of neurology "for students and physicians," according to the author's preface.

For brevity there are no sections on the anatomy nor the examination of the nervous system. The author suggests that special texts on these subjects should be consulted. One might wish that at least an outline of the technique of examination was included since most books limited to that are too detailed for those for whom this book was written.

Diseases are grouped according to etiology as far as possible with certain exceptions such as diseases of the peripheral nerves.

The book is very complete for one this size and well documented by tables of incidence. It is likewise well illustrated and affords a very adequate index. It is heartily recommended by the reviewer as a volume which comes up to the standard one would expect from so outstanding a neurologist.

S. G.

The Abnormal Pneumoencephalogram. By Leo M. Davidoff, M.D., Professor and Chairman, Department of Surgery of the Albert Einstein College of Medicine, and Bernard S. Epstein, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New York. 2nd ed. Pp. 518; 696 ills. Philadelphia: Lea & Febiger, 1955. Price, $15.00.

This book is a valuable companion to the "Normal Encephalogram" by Davidoff and Dyke.

The material is divided into 39 chapters. Each chapter is well organized and includes pertinent references to the literature as well as the authors' material.

The majority of the illustrations are superb and self-explanatory. Incidentally, there are a number that did not reproduce well and it is hoped that the authors will replace these in a subsequent edition.

Cerebral angiography has, in many instances, supplanted pneumoencephalography, particularly in lesions of the cerebral blood vessels. However, as the authors point out, "pneumoencephalography remains as a bulwark in the day to day evaluation of neurological and neurosurgical problems. When properly utilized, it covers a width of diagnostic spectrum not adequately represented by other technical diagnostic aids. . . ."

This book is of particular interest to the neurologist, neurosurgeon and roentgenologist.

M. S.

Radioisotope Conference, 1954. Volume 1. Medical and Physiological Applications. Volume 2. Physical Sciences and Industrial Applications. Edited by J. E. Johnston, R. A. Faires, and R. J. Millett. Pp. 418 and 223; 166 and 75 ills., respectively. New York: Academic Press, Inc., 1954. Price, $16.00 for 2 volumes.

The first volume of this report on the Radioisotope Conference held in 1954 at

Harwell, the National Atomic Energy Laboratory of Great Britain, is devoted to subjects of great interest to the medical sciences. Many of the subjects are reported here for the first time, and others, previously reported elsewhere, are amplified and made considerably more valuable by exceedingly worthwhile discussions by authorities from all over the world.

As an example of some of the subjects covered in the first volume one may cite articles on therapy, including new applicators for the treatment of carcinoma of the cervix, papillomatosis of the bladder, localization of radioactive gold in the lungs, and the relation of the white count in leukemia to P^{32} dosage. In the diagnostic fields, further studies of salivary radioactive iodine concentrations as measures of thyroid function are presented. Also, a study of the turn-over of radioactive iodine in thyroid carcinoma, new studies in scintillation counting techniques, techniques with tracer doses of iron, studies of the uptake of P^{32} as a test of the viability of stored skin, studies on bone metabolism, body sodium, migration of ions across intestinal and bladder mucosa, estimation of vascular sufficiency of muscle, and the like. In the animal physiology section, articles discussing methods of determining cardiac output, blood volume, blood platelet tracing, biosynthesis and so on are covered. Extensive sections on biochemistry are also included.

The authority and scope of the articles presented are of such excellence as to make this volume an essential part of the library of all interested in or dealing with radioactive isotopes, or in clinical or physiological research in general.

Volume 2 of this series is devoted to industrial applications of radioactive isotopes, and while of some interest, is neither directly applicable to or necessary in the medical and biologic sciences. R. R.

BENJAMIN FRANKLIN. SOME ACCOUNT OF THE PENNSYLVANIA HOSPITAL. Printed in Facsimile with an Introduction by I. BERNARD COHEN. Pp. XL and 40, illustrated. Baltimore: Johns Hopkins Press, 1954. Price, $3.25.

HIGH in the list of Benjamin Franklin's benefactions to the world and to Philadelphia in particular stands his role in promoting the Pennsylvania Hospital, the first institution in this country founded for the care of the sick. A prominent part in this role was, as Dr. Cohen emphasizes in his important Introduction, the successful development of Dr. Thomas Bond's original concept, both in the Colonial Assembly and among the public-spirited citizens of Philadelphia. Incidentally, one reads with interest that Philadelphia at that time was becoming the third largest city in the British Empire.

A section of Franklin's Autobiography, quoted at length by Dr. Cohen, describes the shrewd maneuver by which, in 1751, Franklin got the financial support of the Assembly. This "Some Account," prepared by Franklin three years later to stimulate donations for the hospital building that had been planned, rightly constitutes a milestone in our country's medical progress. The backing of private citizens had already been sought in various newspaper articles, which Dr. Cohen says (p. XXI) are not to be found in Franklin's works but are reprinted "in the book here reproduced." As few signs of them can be detected in this Account by at least one reader, a subject for an historical investigation might well be developed from it. In Franklin's text are found not only the steps connected with the founding of the Hospital but also the finances, lists of managers and contributors, a table of cases admitted (lunacy being the next to largest group) and other matters that illumine the state of hospital activities at the time in this country. However still more can be learned about the early workings of the hospital and of Franklin's promotional methods generally from Dr. Cohen's 40-page Introduction. After considering various factors that influenced Franklin's concern with public health such as Defoe's "Essay on Projects" and Cotton Mather's "Essays to Do Good" and Philadelphia's spirit of liberal tolerance, Dr. Cohen surveys in more detail the various histories of the Hospital that have followed this first Account. The original building of 1755 was so quickly outgrown that in 1761 a Committee produced "A Continuation of the Account of the Pennsylvania Hospital" covering the years 1754 to 1761. Franklin was abroad and the Assembly unhelpful, probably the two facts were not unrelated. Both the 1754 Account and its Continuation were reprinted in 1817 "at the office of the United States Gazette." Cohen regards this reprint as rarer than the originals, and has never seen a copy. Neither Account has since been reprinted, though lengthy excerpts have been used in Morton's History of the hospital, Packard's "Some Account," (which entertainingly imitates the title page and general style of the 1754 Account) continued to 1938.

The present volume is the sixth in the Bibliotheca Medica Americana series of the Johns Hopkins Institute of the History of Medicine. It is reproduced from a copy in the De Golyer Collection at the University of Oklahoma, and the text studied from a copy in the Boston Athenaeum. One wonders why the Library of the Hospital itself, with its rich collection of manuscripts and "Some Accounts" apparently was not consulted.

The celebration of the Hospital's bicentenary in 1951 evoked a number of articles all of which recognized Franklin's contribution and several have brought out how well the hospital has followed Franklin's example in progressive pioneering. Dr. Cohen concludes his Introduction with generous references to the hospital's leading position. Many more than Philadelphians should cherish this latest selection by the Hopkins Institute for its monument of American medical history.

E. K.

THE PSYCHIATRIST AND THE DYING PATIENT. By K. R. EISSLER, M.D. Pp. 338; 3 ills. New York: International Universities Press, Inc., 1955. Price, $5.00.

THE author organizes the work into three sections: 1) theoretical concepts of the psychology of death, 2) three case histories illustrating technical problems in the psychiatric treatment of patients approaching death, and 3) concluding remarks in which the author advances psychological foundations for a "proper manner of dying."

The theoretical papers include discussions of Freud's death instinct concept of which Dr. Eissler is a proponent. He points out reasons it is difficult to be objective about death inasmuch as we have strong emotional reactions to the dying patient and we cannot really imagine our own death. The psychology of suicide is reviewed. The prospect of future pleasure is the source of the wish to continue life even for the stoic who has renounced secular pleasure and looks forward only to pleasures in a deity. In the face of permanent loss of pleasure, death may be courted.

One of many provocative questions in the section is: When life ends in suicide we recognize this as the culmination of psychological trends but may not all death be a psychological event growing out of the individual's life history?

In the management of the three patients described the evolution of a planned technique is evidenced. The psychiatrist must feel sorrow and pity without grief or panic. He needs act, paradoxically, as though the patient has a future or is immortal and yet behave in keeping with the gravity of impending death. The patient needs love unadulterated by hostility and evidenced in a feeling that his needs will be ungrudgingly met. A gift will often express the love, the sorrow and yet the belief in the patient's recovery or immortality. The psychiatrist must aid the patient to build a harmonious philosophy consistent with the patient's beliefs and needs.

The therapist thus acts less like a psychiatrist and more like a close friend aided by his experience and insight.

In the presentation of cases and in the conclusion many ethical and emotional problems arising in treatment are discussed with refreshing frankness. In his conclusion, he advocates a realistic approach to death as an ultimate expression of individuality. Dr. Eissler is a clear, concise and interesting writer. He introduces many thoughts which have rarely been expressed and gives new clarity to many better known questions. The work also contains an extensive bibliography. The author satisfies what may be the most important function of a scientific work, to formulate provocative questions. O. E.

A HISTORY OF DERMATOLOGY IN PHILADELPHIA. Written and edited by REUBEN FRIEDMAN, M.D. Pp. 556; 136 ills. Fort Pierce Beach, Florida: Froben Press, Inc., 1955. Price, $10.00.

IT is a good thing to know the men and events of the past, and a laudable instinct to take pride in the participation of local celebrities in the making of history. Dr. Friedman, Clinical Professor of Dermatology at Temple University and a member of the American Association of the History of Medicine, should receive the plaudits of his colleagues for gathering together in this volume not only a great deal about Louis A. Duhring, whom he dubs "Father of Dermatology in Philadelphia," but also many interesting facts pertaining to Philadelphia at the beginning of the Duhring era (1870), as well as a rapid survey of the development of dermatology as a specialty.

Much of the body of the book is composed of altered reprints of biographical sketches of Duhring, Van Harlingen, Stelwagon and others important in the historical development of Philadelphia dermatology. In addition there

are printed long bibliographical lists of papers, a list of Philadelphia Dermatological Society Members in 1951 (five pages of names and addresses), a list ten pages long, of postgraduate students and the like.

The numerous illustrations, which include a number of portraits, consist for the most part of reproductions of dermatological books and papers mainly from the rich resources of the Library of the College of Physicians of Philadelphia.

The book is not meant to be read at one sitting. Its value lies rather in the fact that here are gathered materials in one corpus which the author apparently felt would be useful to dermatologists and medical historians alike. An index would have helped greatly to achieve this purpose. To Philadelphians the work affords added justification for our pride in what we have done and what we are doing in the field of dermatology. S. R.

PSYCHOCUTANEOUS MEDICINE. By MAXIMILIAN E. OBERMAYER, M.D., Clinical Professor and Chairman, Department of Dermatology, School of Medicine, University of Southern California. Pp. 487; 113 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $9.75.

OBERMAYER, a long-time student of psychocutaneous medicine, has made a positive contribution to this phase of medicine. In his book he aimed to define and to assess the important role of the psyche in the causation of, precipitation of, the prolongation of, and the reaction to certain diseases of the skin. The volume contains some historical considerations of the development of psychocutaneous thought and has collected into one place much information that is widely scattered in the literature. The section on dynamic considerations of the psyche by Dr. Richard D. Evans, Associate Clinical Professor of Psychiatry at the School of Medicine of the University of Southern California, supplies for the dermatologist psychiatric knowledge in which he is usually deficient. The reader will also find a discussion on constitutional factors, the theories of mechanisms and methods of study, classification and presentation of more than thirty specific cutaneous diseases in which the psyche is involved to greater or lesser degrees. In addition, there is a discussion of the diagnostic approach and treatment. The book is supplied with a splendid bibliography and index.

This is the second book on this subject which has appeared in English in recent years. It is perhaps the more readable of the two, and certainly the more profusely illustrated. Although Obermayer has opinions of his own on the various items discussed, he does not present the material in a didactic fashion. On the contrary, he makes certain that the opinions of others are available for comparison with his own. The book is beautifully printed and with the exception of several errors in the spelling of names, the reviewer could find nothing to criticize in the matter of typography. This is a volume which should have a special appeal to internists, psychiatrists and dermatologists. H. B.

MODERN TRENDS IN OPHTHALMOLOGY. Edited by ARNOLD SORSBY, Research Professor in Ophthalmology, Royal College of Surgeons of England, Royal Eye Hospital, London. 3rd ed. Pp. 331; 111 ills. New York: Paul B. Hoeber, Inc., 1955. Price, $12.50.

OPHTHALMOLOGISTS, overburdened as they are, with overwhelming clinical loads, are still further overburdened by an ever expanding literature, the evaluation of which, becomes progressively more difficult.

Dr. Sorsby, with the aid of fifty well selected collaborators, has successfully condensed, simplified, and clearly presented, the important and significant trends and advances, in the field, in a fashion which minimizes the task of keeping abreast with the current concepts. No ophthalmologist, who is interested in his subject, can afford to be without this inspiring book.

The reader must constantly remind himself, however, that much of the subject material, while authoritatively presented, is new and has not had the opportunity to stand the test of time. Reasonable reservation must be exercised in evaluating some of the subjects. The pace of progress in other subjects, such as retrolental fibroplasia, is such that parts of the presentation are already obsolete. The technique for the binocular indirect ophthalmoscope is oversimplified. In spite of other minor criticisms, this book is extremely welcome. G. G.

FRACTURES IN CHILDREN. By WALTER P. BLOUNT, M.D., F.A.C.S., Chairman of Orthopedic Section, Milwaukee Children's Hospital. Pp. 279; 311 ills. Baltimore: Williams & Wilkins Co., 1954. Price, $9.50.

UNTIL Dr. Blount published this text, there was a paucity and almost an absence of texts

devoted only to fractures in children. The majority of texts concerned themselves with fractures primarily in the adult. Many of these practically omitted the management of fractures in the child. Amongst the very many journals the management of fractures seems to be concentrated on plates, screws, and other types of hardware to maintain fracture reduction. Dr. Blount's text stresses the importance of conservatism in most fractures of the child and, by contrast, it is most refreshing.

The coverage is comprehensive; the illustrations are apt and profuse. The cartoons used to stress faulty and overly enthusiastic physiotherapy and rehabilitation are not only unique but most effective.

In the opinion of the reviewer this excellent text should be a "must" for medical students, interns, pediatricians, surgeons and orthopedists. A. S.

MODERN TRENDS IN PSYCHOSOMATIC MEDICINE. Edited by DESMOND O'NEILL, St. Mary's Hospital. Pp. 375; 29 ills. New York: Paul B. Hoeber, Inc., 1955. Price, $10.50.

LIKE so many multi-authored books this British contribution to psychosomatic medicine is unevenly written. For the most part the contributions do not reflect the level of attainment that psychosomatic medicine has achieved in the United States. A number of the chapters are exhortative, in a manner comparable to American articles on psychosomatic medicine of 20 years ago. Among the best of these is the first chapter by Philip Hopkins which has to do with the general practitioner and the psychosomatic approach.

An interesting chapter on emotions and eye symptoms is contributed by W. S. Inman. This was first published in the year 1921 and the editor wisely includes it. It shows that there were observant physicians, who were well aware of the role of emotional factors in illness at that time, had orthodox medicine been wise enough to follow them. Among the contributions which have something new to say is one by Markillie on group psychotherapy in psychosomatic disorders. There are also interesting observations on hypertension by Hambling. But other chapters are speculative and fantastic, for example, a chapter on music and migraine, which is amusing and well written but hardly deserves a place in a serious work. The subject of anxiety and muscle tension is dealt with in a chapter on posture training so that the book in addition to being unevenly written, represents many different points of view, not all of them acceptable to the person trained in psychodynamics.

There have been noteworthy contributions to psychosomatic medicine from Great Britain and it is unfortunate that names such as Halliday, and Macalpine, who have fresh and interesting viewpionts and have published important papers are missing from this book.

Although the term psychological medicine has been used in Great Britain for a longer period of time than psychosomatic medicine in the United States, it has not meant the same thing so that this book, specifically dealing with the relation of emotional factors to bodily illness, in spite of its shortcomings, is welcome as one of the few contributions on this subject from Great Britain. E. W.

LEHRBUCH DER RÖNTGENOLOGISCHEN DIFFERENTIALDIAGNOSTIK. VOL. 2. BY WERNER TESCHENDORF, Cologne. 3rd ed. Pp. 1037; 1610 ills. Stuttgart: Georg Thieme Verlag, 1954 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $44.30.

IN this new edition the number of illustrations has been greatly increased; and the text has been much altered (pancreas, cholangiography) and newly written (retropneumoperitoneum, aortography, portal angiography). References abound and are arranged at the bottom of the pages, while the topic under discussion appears as marginal print. The vastness of the material covered can be gauged by the fact that the list of topics, as given in the table of contents, comprises 5 pages in small print. The quality of the illustrations (they represent a museum of pathology) and of the print is of the highest type. All radiologic signs of the great variety of abdominal diseases are evaluated in their diagnostic and differential diagnostic significance. Anatomical, physiological and clinical data are well integrated. Diagnostic and therapeutic management of the patient ill with abdominal disease calls on a variety of specialists, in addition to the practitioner. Teschendorf's book offers much and very valuable information to everyone who will consult it. Unfortunately, the time has passed long ago when a scientist wrote in Latin and was understood readily by his confreres; perhaps some day Interlingua will be the answer; in the meantime translation of this book into English would be a valuable contribution to the science and practice of medicine. H. R.

THE CLINICAL EXAMINATION OF THE NERVOUS SYSTEM. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor of Medicine, University of Oslo. 10th ed. Pp. 428; 165 ills. New York: Paul B. Hoeber, Inc., 1955. Price, $7.50.

THE present edition amply gives evidence of the growth and development of Neurology since this is more than twice the size of the third edition of 1926 which is part of the reviewer's library. In no other book can the material here offered be found so completely and thoroughly discussed. The appendix affords consideration of psychologic testing, examination for aphasia, interpretation of roentgenograms of the skull including ventriculogram, encephalogram and angiogram and electroencephalogram and electromyogram. While these are admittedly not encyclopedic in scope, they are excellent.

The sincere student of neurology, be he medical student, intern, graduate student, neurologist or neurosurgeon, cannot afford to be without it. The psychiatrist practicing away from the large centers where he has to help care for neurologic patients as well as the internist who has to do the same thing, should consider this book a must. The reviewer most heartily recommends this product of the mind of this most distinguished and world famous neurologist.

The author cannot resist the voicing of the fear, expressed by others of the older group of neurologists, that "technical supplementary methods of examination" may "blunt the young neurologist's interest for clinical observation and for the patient as an individual."

S. G.

THE CLINICAL INTERVIEW. VOLUME 2: THERAPY: A METHOD OF TEACHING SECTOR PSYCHOTHERAPY. By FELIX DEUTSCH, M.D., and WILLIAM F. MURPHY, M.D. Pp. 335. New York: International Universities Press, Inc., 1955. Price, $7.50.

THIS volume is primarily directed to psychotherapists and those who train them. Some understanding of Freudian concepts and terminology is requisite for learning the use of sector therapy. The authors' premises are:

1) Students request and need a well-structured psychotherapy to help them understand and treat patients.

2) "Sector therapy" in its use of "directed free associations" in a limited area elucidates the unconscious significance of what the patient is saying. This is the basis for treatment in depth of a limited area of the personality.

3) This elucidation makes the effect of the unconscious concretely apparent to the therapist, and may be appropriately communicated to the patient in the terms of his verbalizations after a positive relationship is established.

4) Each interview has a unity of its own in which there is an attempt to ally with the more mature part of the individual's personality to strengthen it in facing the infantile component.

Recorded interviews (which constitute the bulk of the book) make the therapeutic situation and the discussion of it more realistic. The psychologic formulations which form the basis for the supportive, reassuring, confronting, and interpreting remarks of the therapist are given. As with any technique, it must be incorporated into the personality of the therapist so it is not recognizable as a technique.

O. E.

LEITFADEN DER ÖRTLICHEN BETÄUBUNG. By PROF. DR. ERNST SEIFERT, Formerly Director, Surgical Clinic, University of Würzburg. Pp. 195; 31 ills. Munich: J. F. Lehmanns Verlag, 1955. Price, DM 12.20.

OUTSTANDING is Dr. Seifert's section on caudal block, epidural anesthesia and brachial block.

The author's intimate knowledge of Läwen's technique and experience lends authority to his discussion of caudal anesthesia.

It is refreshing to read a comprehensive, straightforward delineation of epidural anesthesia. Dogliotti's technique is described in detail. More specifically, the mode of action of epidural anesthesia, the hazard of inadvertant dural puncture, and the pitfalls of disruption of the epidural venous plexus are discussed at length. The author stresses the essence of success depends upon the site of entry into the epidural space.

Conspicuous by its absence is mention of the elbow and wrist block as a suitable substitute for brachial block when indicated.

Despite the paucity of illustrations, there are repeated references to fundamental pertinent anatomy. A more complete presentation of the role of regional anesthesia in diagnostics and therapeusis would be desirable.

This manual offers a quick, fact-packed review of regional anesthesia, basically including the pharmacology, toxicology, and clinical applications and limitations of the local anesthetic agents in popular use today.

E. C.

KREISLAUFREGULATION. BY H. REINDELL, E. SCHILDGE, H. KLEPZIG, and H. W. KIRCHHOFF, Freiburg. Pp. 315; 69 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $9.90.

THE book starts out with an excellent presentation of the physiology of the circulation analyzing all the many interplaying factors. Then follows a discussion of faulty vegetative regulation with particular emphasis on the effects of our civilization, and of the psyche. Types of circulatory disturbances induced by way of the vegetative system are described; such as fainting and shock, circulatory reaction secondary to cardiac infarction, psychic effects, hypotonic and hypertonic states. Faulty regulation can alter the metabolism of the heart muscle. Complaints of the patient on a vegetative basis are discussed, with particular reference to pain; the chapter on anxiety is outstanding. A general psychosomatic discussion is strengthened by detailed case reports, and electrocardiographic and hemodynamic studies in conjunction with hypnosis are presented (the changes described for the electrocardiograms, leads I, II, III, only being used, are not always convincing to the reviewer, neither here nor in the subsequent chapter on prognostic considerations).

The chapter on the therapeutics of circulatory disturbances of vegetative and psychic origin offers many practical points; it is rightfully pointed out that the choice of therapy is influenced by the physician's concepts, empiricism and training. This monograph is well recommended to physiologists and clinicians. H. R.

MENTAL HEALTH AND HUMAN RELATIONS IN INDUSTRY. Edited by T. M. LING, M.A., D.M.(OXON.), M.R.C.P. Pp. 265; illustrated. New York: Paul B. Hoeber, Inc., 1955. Price, $6.00.

THIS is an interesting, informative and timely book on mental health written at a time when the greatest stress is being placed upon the need for a consideration of factors which will bring about a greater degree of personality health. The author is well able to treat this subject having spent many years in a center devoted to rehabilitation. He invites the reader to give more consideration as to how far a man's job meets his emotional needs and he puts a mental health challenge to industry when he says "Industries are easier to modify than cities so it is to be hoped that the former will increasingly develop a social structure suitable for the maturation of the human personality."

There are many interesting themes treated in a total of 14 chapters some of these being, "Psychological and Occupational Effects of Illness and Accident," "Aggression in Industry," "The Importance of Selection and Allied Procedure," "The Working Environment" and a concluding chapter on "Implications for Management." This is one of the most succinct and, at the same time, clear and inclusive books on this important field of medicine for the internist, psychiatrist, industrialist or any person working in this field. O. E.

FOURTH ANNUAL REPORT ON STRESS. BY HANS SELYE, M.D., and GUNNAR HEUSER, M.D. Pp. 749; illustrated. Montreal: Acta, Inc., 1954. Price, $14.75.

THE Fourth Annual Report on Stress is a valuable addition to the library of the practicing physician who is interested in this extremely important aspect of medicine. Advances which have been made during the year have been incorporated in this volume and modifications as well as additions to the concept of stress are included. As in past issues separate sections are devoted not only to the endocrine system but also to bones, joints, blood and organ systems. W. P.

NEW BOOKS

The Biochemistry of Semen. BY T. MANN, M.D., SC.D., PH.D., F.R.S., University of Cambridge. Pp. 240; 23 ills. New York: John Wiley & Sons, Inc. (London: Meuthen & Co., Ltd.), 1954. Price, $2.90.

THIS little book fills a definite need for a summary of the current knowledge of the chemistry of the constituents of semen. The author and his colleagues at Cambridge have contributed much to our present knowledge of this important subject. Those interested in fertility and related problems in almost any species should find this little book of considerable value.

The book may be regarded as authoritative. It is well written and amply notated. There are 28 pages of literature references included at the end. Two comparatively minor points one may note are that others have been unable to repeat Mann's work on the biogenesis of the ergothioneine in boar semen, and that the role of this sulfhydryl compound may not be what is assumed in this book.

The chapter headings include I. The Two Components of Semen: Spermatozoa and Seminal Plasma (included are photomicrographs of bull and rat sperm and an electron micrograph of sperm-tail); II. Chemical and Physical Properties of Whole Ejaculated Semen; III. The Influence of Extraneous Factors, Hormones and Environmental Conditions; IV. Intracellular En-

zymes, Metalloproteins, Nucleoproteins and Other Protein Constituents of Spermatozoa; V. Protein Constituents and Enzymes of the Seminal Plasma; VI. Lipids and Their Role in the Metabolism of Semen; VII. Fructose and Fructolysis; VIII. Spermine, Choline, Ergothioneine and Certain Other Bases in Semen (including a photograph of a drawing of spermine phosphate crystals drawn by Leeuwenhoek in 1677); XI. Citric Acid and Inositol. R. B.

Introduction to Thermodynamics of Irreversible Processes. By I. PRIGOGINE, D.Sc., Professor, Faculty of Science, University of Brussels. Pp. 115. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.75.

I Cured My Cancer. By MARY PAYNE, R.T. Pp. 69. New York: Vantage Press, Inc., 1955. Price, $2.50.

THIS is the somewhat gossipy account of the author's feelings as she learns of advanced pelvic cancer and goes through successful radiation therapy. She eventually trains as a Roentgen-ray technician with the radiologist who treated her. H. S.

The Relation of Immunology to Tissue Homotransplantation. By JOHN MARQUIS CONVERSE, O. ROGERS BLAIR AND OTHERS. Annals of the New York Academy of Science, Vol. 59, Art. 3. Pp. 190; illustrated. New York: New York Academy of Science, 1955. Price, $4.00.

Ionizing Radiation and the Cell. By LESLIE F. NIMS and 22 OTHERS. Annals of the New York Academy of Science, Vol. 59, Art. 4. Pp. 200; illustrated. New York: New York Academy of Science, 1955. Price, $4.00.

A Therapeutic Index. By C. M. MILLER, M.D. (LONDON) M.R.C.P. (LONDON), Consultant Physician, Sefton General Hospital, Liverpool; and B. K. ELLENBOGEN, M.D. (LIVERPOOL) M.R.C.P. (LONDON); Senior Medical Registrar, Royal Southern Hospital, Liverpool. Pp. 148. London: Bailliere, Tindall and Cox, 1955. (The Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $3.75.

WRITTEN for a ready treatment reference for hospital residents and general practitioners, this book contains many conditions such as obesity, myotonia congenita, Hodgkin's disease, among others, that utilize space which could be employed for other conditions needing more immediate treatment. Some of the more recent important therapeutic agents such as hydrocortisone and edathamil calcium-disodium are not mentioned by the authors, perhaps because they have had no personal experience with their use. I. G.

Amphetamine in Clinical Medicine. Actions and Uses. By W. R. BETT, L. H. HOWELLS, and A. D. MACDONALD, Pp. 78. Edinburgh and London: E. & S. Livingstone, Ltd., 1955 (The Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $2.75.

THE drug, amphetamine, is discussed from the standpoint of its development and pharmacology in a concise manner in the introductory chapters. The familiar use of the agent as anorexigenic factor in weight reduction programs is reviewed, with additional details of treatment including a dietary regimen. Further uses of the drug are presented in the management of fatigue and depression, narcolepsy, alcoholism and drug addiction, psychopathic states, enuresis and behavior disorders in children. The text is written in an engaging and informative fashion and will be of assistance to the clinician employing the amphetamine group of drugs. C. S.

Standard Values in Nutrition and Metabolism. Edited by ERRETT C. ALBRITTON. Pp. 380. Wright-Patterson Air Force Base, Ohio: Wright Air Development Center, Air Research and Development Command, U. S. Air Force, 1954.

Komplexe Psychologie und körperliches Symptom. By PROF. DR. GUSTAV SCHMALTZ. Pp. 118; 4 ills. Stuttgart: Hippokrates-Verlag, 1955. Price, DM 8.80.

THIS is a short account of the psychotherapy of a case of angina pectoris in cooperation with an internist. There is a short foreword by Jung and the therapeutic orientation developed follows the Jungian pattern. Although the author writes a detailed outline of the progress of treatment, little that is new concerning psychodynamics or technique of treatment is developed. S. H.

Röntgendiagnostik des Schädels. By PROF. DR. WILLY LOEPP and PROF. DR. REINHOLD LORENZ. Pp. 579; 613 ills. Stuttgart: Georg Thieme Verlag, 1954. Price, DM 97.

AN excellent text on an important phase of radiologic diagnosis. The numerous illustrations are extremely well done. R. K.

Leukocytic Functions. By Albert S. Gordon, John W. Rebuck, and Robert S. Speirs, and others. Pp. 406; illustrated. New York: New York Academy of Sciences, 1955. Price, $4.50.

NEW EDITIONS

Microbiology. By Florence C. Kelly, M.S., Ph.D., and K. Eileen Hite, University of Oklahoma School of Medicine. 2nd ed. Pp. 615; 185 ills. New York: Appleton-Century-Crofts, Inc., 1955. Price, $7.50.

The first edition of this textbook appeared in 1949 and was well received as a "little book" containing the essentials of the subject. The second edition is the same size and in fact retains unchanged much of the previous subject matter. Certainly, the approach is the same and so it is surprising that the authors in the preface say it "is intended for the student who will require a comprehensive knowledge. . . ." The book is not that informative. For example, the treatment of hypersensitivity is most superficial, hardly informative at all and practically identical with that in the first edition except for the insertion of the Shwartzman phenomenon which, incidentally, is not known to be concerned with hypersensitivity. This reviewer searched in vain for mention of such currently important procedures as antistreptolysin and C-reactive protein tests, and for a discussion of the "pathogenic E. coli" strains in epidemic diarrhea of the newborn.

These adverse remarks should not be construed to mean that this text is entirely inadequate for it will continue to be a popular text with students of medical technology and sciences allied to medicine. And it is recommended, provided that the instructor is prepared to take up where this book leaves off. By and large the factual material is accurate and carefully phrased.

The kind of type, quality of paper and general format are very satisfactory indeed, although the need to waste space by standing illustrations on end (as on page 414) is not apparent.

E. S.

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Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

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